FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

Meeting Date:	23 May 2012
NDA:	202439/S-002
Sponsor:	Janssen Pharmaceuticals, Inc.
Drug:	Xarelto® (Rivaroxaban) oral tablets
Indication for Use:	To reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) [ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA)] in combination with aspirin alone or with aspirin plus clopidogrel or ticlopidine.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the rivaroxaban New Drug Application (NDA) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Topics for Discussion

Rivaroxaban

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

The Advisory Committee is asked to opine on the approvability of rivaroxaban (2.5 mg BID) to reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) [ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UA). During today's meeting, the Committee will be presented with the results of the development program for ACS for rivaroxaban, a factor Xa inhibitor already approved for deep vein thrombosis and atrial fibrillation indications.

The support for this claim comes from

1) RIVAROXACS3001, "A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects With a Recent Acute Coronary Syndrome" (The ATLAS ACS 2 TIMI 51 Trial (The second trial of *A*nti-Xa *T*herapy to *L*ower cardiovascular events in *A*ddition to standard therapy in *S*ubjects with *A*cute *C*oronary *S*yndrome) (Phase 3 trial in 15,526 subjects) and
2) RIVAROXACS2001, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Escalation and Dose-Confirmation Study to Evaluate the Safety and Efficacy of Rivaroxaban in Combination with Aspirin Alone or with Aspirin and a Thienopyridine in Subjects with Acute Coronary Syndromes (The ATLAS ACS TIMI 46 Trial (*A*nti-Xa *T*herapy to *L*ower cardiovascular events in addition to *A*spirin with or without thienopyridine therapy in *S*ubjects with *A*cute *C*oronary *S*yndrome) (Phase 2 trial in 3491 subjects)

1. RIVAROXACS301, the ATLAS ACS trial, had substantial missing data. Poor follow-up, predominantly attributed to withdrawal of consent, has been a distressing trend in recent CV outcomes trials.
    1.1. Please discuss how the quality of a study, the missing follow-up and other data problems, should be factored into the interpretation of study results.
    1.2. Should the FDA pre-specify trial standards for data quality just as we pre-specify standards for p values, e.g., x rate of missing data may lead to nonapproval regardless of p value?
    1.3. Documentation of withdrawal of consent has been minimal. What documentation regarding withdrawal of consent should be required?
    1.4. Documentation of final contacts has been inconsistent.
        1.4.1. What documentation regarding contacts, for both office visits and phone calls, should be required?
        1.4.2. How should it differ for vital status follow-up compared to follow-up for other endpoints.
    1.5. What measures of completeness of follow-up should be included in the primary study publication?
    1.6. Please discuss any other suggestions regarding how trial follow-up may be improved, in particular those that the FDA can influence.
2. Please comment on the statistical analysis plan for ATLAS.
    2.1. Please discuss the merits and pitfalls of a "modified-Intent-to-Treat" (on-treatment plus 30 days) compared to an Intent-to-Treat analysis for superiority of efficacy endpoints.
    2.2. Given the description in the Statistical Analysis Plan with respect to testing the secondary endpoints, please discuss which strata and which endpoints, if any, should be considered for label claims
    2.3. Given the late changes in the SAP to exclude Sites 091001, 091019, and 091026, what should the primary analysis population be for this trial—including or excluding these sites?

2.4. In general, how should sites that have issues with proper documentation but have sufficient data to adjudicate events be managed from a clinical and statistical standpoint?

3. Please comment on the *effectiveness* of rivaroxaban

3.1. How should the data quality issues in ATLAS, including 1294 subjects who discontinued prematurely from the study, incomplete follow-up, missing vital status, and uncounted deaths, be factored into the study interpretation?

3.2. The efficacy results appear to be inconsistent, with rivaroxaban 2.5 mg BID primarily reducing CV deaths and rivaroxaban 5 mg BID primarily reducing MIs.

3.2.1. Do you consider these findings to be biologically plausible?

3.3. In the small stratum for aspirin use alone without a thienopyridine, rivaroxaban 2.5 mg BID primarily reduced MIs while increasing CV deaths and rivaroxaban 5 mg BID reduced both CV deaths and MI.

3.3.1. Are there sufficient data to conclude rivaroxaban 2.5 mg BID would be beneficial in this population (aspirin but no thienopyridine) or that its effects differ than when combined with clopidogrel or ticlopidine?

3.3.2. Is rivaroxaban 2.5 mg BID the appropriate dose for this population (Stratum 1) or do the data suggest that a higher dose of rivaroxaban (5 mg BID) may be needed?

4. Please comment on specific safety issues of

4.1. Bleeding and particular populations that are most susceptible to this risk.

4.2. Increased susceptibility of ACS patients to drug-induced liver injury.

4.3. Lack of efficacy in subjects with a prior history of ischemic stroke or TIA.

5. Please comment on the net clinical benefit of rivaroxaban

5.1. In the Advisory Committee Briefing Package, the sponsor has provided benefit-risk analyses on pages 130-131.

5.1.1. Do you agree with how the sponsor has broken down efficacy and safety events in this analysis?. If no, what other factors would be critical to include in such an analysis when considering benefit-risk assessments for rivaroxaban?

6. [VOTE] Should rivaroxaban be approved for ACS?

7. If you voted for approval, comment on the following label issues:

   7.1. What should be the wording of the indication?

      7.1.1. Is reduction of the risk if CV thrombotic events the appropriate wording?

      7.1.2. Should there be an explicit mortality claim?

      7.1.3. Does bleeding risk warrant a box warning? If so, what language should be used to describe bleeding risk?

   7.2. Are there any subgroups for which rivaroxaban should not be recommended, e.g., patients with a prior history of ischemic stroke or TIA?

   7.3. What should be the recommendation regarding use with aspirin alone?

   7.4. How, and in which label sections, should use with prasugrel and ticagrelor be described?

8. If rivaroxaban is approved, will you use this drug for ACS patients in clinical practice?

   8.1. If so, who are the optimal candidates for rivaroxaban?

   8.2. If not, why not?

CLINICAL REVIEW

Application Type	S-NDA (505 (b) (1))
Application Number(s)	202,439 (S-002, Sequence No. 125)
Priority or Standard	Priority
Submit Date(s)	December 29, 2011
Received Date(s)	December 29, 2011
PDUFA Goal Date	June 29, 2012
Division / Office	DCaRP/ODE 1
Reviewer Name(s)	Karen A. Hicks, M.D.
Review Completion Date	April 30, 2012
Established Name	Rivaroxaban
(Proposed) Trade Name	Xarelto®
Therapeutic Class	Anticoagulant (Factor Xa inhibitor)
Applicant	Janssen Pharmaceuticals, Inc.
Formulation(s)	Oral tablet – 2.5 mg
Dosing Regimen	2.5 mg orally twice daily
Indication(s)	To reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of XARELTO® (2.5 mg po BID) to reduce the risk of cardiovascular events in patients with acute coronary syndrome (ACS) [ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UA)] who are to be managed with aspirin plus clopidogrel or ticlopidine.

XARELTO® (2.5 mg po BID) has been shown to reduce the rate of a combined endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke, compared to placebo, when administered in addition to standard care consisting of aspirin plus either clopidogrel or ticlopidine. The difference between treatments was driven predominantly by cardiovascular death, with little difference on myocardial infarction and no difference on ischemic stroke.

The following results from the ATLAS ACS 2 TIMI 51 Trial support this recommendation:

1) In All Strata, including subjects treated with aspirin (Stratum 1) and subjects treated with aspirin plus a thienopyridine (Stratum 2), on-treatment plus 30 days (sponsor's modified intent-to-treat (mITT)) and intent-to-treat (ITT) analyses including and excluding Sites 091001, 091019, and 091026 demonstrated that rivaroxaban (combined,[1] 2.5 mg BID, and 5 mg BID) significantly reduced the occurrence of the composite primary endpoint of cardiovascular death, myocardial infarction, or stroke, compared with placebo, in ACS subjects stabilized 1-7 days post index event, as summarized in Table 1. Numerous sensitivity analyses confirmed these results.

[1]**Rivaroxaban combined = rivaroxaban 2.5 mg BID dose group + rivaroxaban 5 mg BID dose group**

Table 1. Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (All Strata)

ALL STRATA	Combined		Rivaroxaban 2.5 mg BID		Rivaroxaban 5 mg BID	
Analysis Set	**HR 95% CI**	**P-value**	**HR 95% CI**	**P-value**	**HR 95% CI**	**P-value**
mITT* excluding Sites 091001, 091019, and 091026	0.84 (0.74, 0.96)	0.008	0.84 (0.72, 0.97)	0.02	0.85 (0.73, 0.98)	0.029
mITT* including Sites 091001, 091019, and 091026	0.85 (0.75, 0.96)	0.011	0.84 (0.72, 0.97)	0.02	0.86 (0.74, 1.00)	0.045
ITT excluding Sites 091001, 091019, and 091026	0.83 (0.73, 0.93)	0.002	0.82 (0.71, 0.95)	0.007	0.83 (0.72, 0.96)	0.011
ITT including Sites 091001, 091019, and 091026	0.83 (0.74, 0.94)	0.003	0.82 (0.71, 0.95)	0.007	0.84 (0.73, 0.97)	0.017

***Sponsor's mITT analysis is an on-treatment plus 30 days analysis**
BID: twice daily; HR: hazard ratio; CEC: Clinical Events Committee; CI: confidence interval; ITT: intent-to- treat; mITT: modified intent-to-treat
Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

2) In Stratum 2 (subjects treated with aspirin plus a thienopyridine), rivaroxaban (combined and 2.5 mg BID) significantly reduced the occurrence of the primary endpoint. Rivaroxaban 5 mg BID was not statistically significant in reducing the occurrence of the primary endpoint.

Table 2. Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (Stratum 2)

STRATUM 2 (Aspirin + Thienopyridine)	Combined		Rivaroxaban 2.5 mg BID		Rivaroxaban 5 mg BID	
Analysis Set	**HR 95% CI**	**P-value**	**HR 95% CI**	**P-value**	**HR 95% CI**	**P-value**
mITT* excluding Sites 091001, 091019, and 091026	0.86 (0.75, 0.98)	0.025	0.85 (0.72, 0.99)	0.039	0.87 (0.74, 1.02)	0.076
mITT* including Sites 091001, 091019, and 091026	0.86 (0.76, 0.99)	0.032	0.85 (0.72, 0.99)	0.038	0.88 (0.75, 1.03)	0.11
ITT excluding Sites 091001, 091019, and 091026	0.83 (0.73, 0.94)	0.004	0.82 (0.71, 0.96)	0.011	0.84 (0.72, 0.97)	0.02
ITT including Sites 091001, 091019, and 091026	0.84 (0.74, 0.95)	0.006	0.82 (0.71, 0.96)	0.011	0.85 (0.73, 0.99)	0.031

***Sponsor's mITT analysis is an on-treatment plus 30 days analysis**
BID: twice daily; CI: confidence interval; HR: hazard ratio; ITT: intent-to- treat; mITT: modified intent-to-treat
Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

3) The findings in All Strata and Stratum 2 were driven primarily by a reduction in CV deaths, particularly on rivaroxaban 2.5 mg BID, and to a lesser extent by a reduction in MI.

4) Compared to 2.5 mg BID, rivaroxaban 5 mg BID increased the risk of all bleeding events without providing additional efficacy. Further, rivaroxaban 5 mg BID improved MI but not CV death which was somewhat unexpected.

5) With respect to reducing all-cause mortality, rivaroxaban 2.5 mg BID was nominally statistically significant. However, rivaroxaban 5 mg BID was not effective and combined rivaroxaban doses were not robust statistically in reducing all-cause mortality. The interpretation of the mortality findings depended on which analysis sets were used and whether sites 091001, 091019, and 091026 were included.

6) Given the inconsistent results between rivaroxaban 2.5 mg BID and rivaroxaban 5 mg BID with respect to CV death and all-cause mortality, I do not recommend a mortality claim.

7) Given the small sample size, data from ATLAS and TIMI 46 are insufficient to determine whether the use of rivaroxaban 2.5 mg BID in Stratum 1 subjects (aspirin) would be beneficial. These subjects may need rivaroxaban 5 mg BID or a $P2Y_{12}$ inhibitor instead.

Prior to arriving at my recommendation above, I also considered the following arguments against approval:

1) In All Strata, a total of 2402 (15.5%) subjects discontinued from the study prematurely, including 1294 (8%) subjects who "withdrew consent." There were over 1000 subjects at the end of the trial with unknown vital status. Additionally, there was incomplete follow-up and uncounted deaths. The quantity of missing data in ATLAS could affect the overall interpretability of the trial.

   Counterargument: Unfortunately, data quality issues are not limited to this trial and have been a concern for several trials in the Division of Cardiovascular and Renal Products over the last several years. Still, this trend does not make the amount of missing data in ATLAS acceptable.

   I decided to recommend approval for the following reasons:

   - I read the Independent Data Monitoring Committee (IDMC) minutes. The sponsor recognized the withdrawn consents were a problem and made a reasonable effort to obtain vital status information on these subjects. Although the results fell short of what needed to be accomplished, 177 additional subjects were confirmed alive.

- I read the sponsor's responses to the FDA information requests and in most cases, the sponsor admitted when mistakes were made or boxes were mischecked by trial personnel.

- I sent the Division of Scientific Investigations' (DSI) representative to Russia to investigate some issues that the sponsor had identified, and the representative confirmed these issues to be true.

2) In general, the ATLAS results demonstrated inconsistent findings between strata and doses and raised questions about the biologic plausibility of the study results. While rivaroxaban 2.5 mg BID primarily had an effect on CV death (i.e., sudden death), with little effect on MI and no effect on ischemic stroke, rivaroxaban 5 mg BID primarily had an effect on MI with little effect on CV death but also resulted in increased bleeding rates compared to rivaroxaban 2.5 mg BID. Generally, one would expect an anticoagulant to affect thrombotic events such as MI or ischemic stroke.

   Counterargument: In ATLAS, not all patients underwent index percutaneous coronary intervention. As a result, early thrombotic events could have been missed since the median time from index event to randomization in ATLAS was approximately 5 days. This theory could also explain why there were numerically fewer MIs in ATLAS, compared to other ACS trials in which patients underwent index PCI. As for CV death reduction on rivaroxaban 2.5 mg BID, a concern is that this finding could be due to chance. However, the primary endpoint results were confirmed in numerous sensitivity analyses, and I am not recommending a mortality claim.

For the reasons stated above, I recommend approval. Should additional information become evident in the next two months that affect overall trial interpretability, I may choose to reconsider this recommendation.

1.2 Risk Benefit Assessment

The assessment of risk and benefit is derived from the sponsor's global study No. RIVAROXACS3001, "A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects With a Recent Acute Coronary Syndrome" (The ATLAS ACS 2 TIMI 51 Trial (The second trial of *A*nti-Xa *T*herapy to *L*ower cardiovascular events in *A*ddition to standard therapy in *S*ubjects with *A*cute *C*oronary *S*yndrome)).

It is interesting to note that the sponsor's assessment of net clinical outcome, a prespecified secondary endpoint defined as the composite of CV death, MI, ischemic stroke, or TIMI major bleeding event not associated with coronary artery bypass graft (CABG) surgery, was numerically but not statistically favorable for rivaroxaban in All

Strata and individual stratum, largely because the increase in non-CABG-related bleeding offset any benefit seen with rivaroxaban on CV death or MI. Please see Section 6 of this review for full details of these analyses.

Fundamental limitations to this approach were that these were unweighted analyses that did not use annualized event rates. These analyses also did not necessarily focus on events that were fatal or that lead to irreversible harm. Most individuals would consider decreases in cardiovascular death and myocardial infarction to outweigh increases in non-fatal non-intracranial bleeding events. Others who consider quality of life to be more important may not agree.

In the Advisory Committee Briefing packet, the sponsor provided a more sophisticated analysis to assess net clinical benefit. Compared to Stratum 1 (aspirin), Stratum 2 (aspirin + thienopyridine) reflects current treatment of ACS patients in the United States and provides a more realistic population from which to assess bleeding risk. Therefore, I will focus my comments on the sponsor's Stratum 2 analysis on rivaroxaban 2.5 mg BID.

Under efficacy, the sponsor included non-bleeding CV deaths, MI, or ischemic stroke while under safety, the sponsor included TIMI Life-Threatening bleeding and TIMI Major bleeding. These bleeding events were not mutually exclusive. TIMI life-threatening bleeding included those events that were fatal; led to hypotension requiring treatment with intravenous inotropic agents; required surgical intervention for ongoing bleeding; necessitated the transfusion of 4 or more units of blood (whole blood or packed red blood cells) over a 48-hour period; or symptomatic intracranial hemorrhage. TIMI Major bleeding included any symptomatic intracranial hemorrhage or clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of ≥ 5 g/dL (or when the hemoglobin concentration was not available, an absolute drop in hematocrit of ≥ 15%). The results of this analysis are displayed in Table 3.

In Stratum 2, rivaroxaban 2.5 mg BID prevented 115 (95% CI: 18, 212) non-bleeding CV deaths, MIs, or ischemic strokes per 10,000 patient-years while causing 74 TIMI Life-Threatening bleeding + TIMI Major bleeding events, including 10 fatal bleeding and symptomatic intracranial hemorrhage events. Rivaroxaban also caused 30 non-fatal, non-ICH TIMI Life-Threatening bleeding events and 38 TIMI Major bleeding, non-life threatening events per 10,000 patient years. From a number-needed-treat (NNT)/number-needed-to-harm (NNH) perspective, treatment of ACS patients with rivaroxaban 2.5 mg BID instead of placebo would result in 1 fewer non-bleeding CV death, MI, or ischemic stroke event per 87 patient-years, while there would be 1 additional fatal bleeding or ICH event every 984 patient-years.

Overall, the benefit risk ratio for XARELTO® (2.5 mg po BID) appears to be favorable, predominantly because there is a reduction in CV death, despite an increased risk of

Table 3. Sponsor's Analysis: Decomposition of Ischemic and Hemorrhagic Events: mITT (Excluding Sites 091001, 091019, and 091026). Rivaroxaban 2.5 mg BID Compared to Placebo (Stratum 2)

Time to Event Category	Endpoints	Event Rate[a] (\ 100 Patient-Years)		Excess Number of Events Rivaroxaban - Placebo		
		Rivaroxaban 2.5 mg BID	Placebo	Excess # events for 10,000 pt-yrs	95% CI	NNT/NNH[b]
Efficacy	Non-bleeding CV death, MI, or ischemic stroke	5.48	6.63	-115*	(-212, -18)	-87
	Non-bleeding CV death	1.48	2.43	-95*	(-149, -41)	-105
	MI excluding CV death	3.59	3.81	-22	(-97, 54)	-462
	Ischemic stroke excluding CV death	0.55	0.51	5	(-24, 33)	2150
	Non-CV death excluding fatal bleed	0.16	0.17	-2	(-19, 15)	-5790
Safety	TIMI life-threatening bleeding + TIMI major bleeding	1.48	0.74	74*	(33, 116)	135
	Fatal Bleeding + symptomatic ICH	0.33	0.23	10	(-11, 32)	984
	Fatal Bleeding	0.16	0.19	-4	(-21, 14)	-2726
	Intracranial Bleeding (ICH)	0.28	0.12	16	(-2, 34)	629
	Fatal ICH	0.10	0.08	2	(-11, 15)	4819
	Non-fatal ICH	0.18	0.04	14	(-1, 28)	723
	Non-fatal, non-ICH TIMI life-threatening bleeding	0.53	0.23	30*	(5, 55)	334
	TIMI major bleeding, non-life-threatening	0.65	0.27	38*	(11, 65)	264

[a]Event rate (/100 Patient-years): Number of events per 100 patient years of follow-up.
[b]A negative number denotes the number of patient years needed to be treated with rivaroxaban instead of placebo to prevent one additional harmful event (NNT). A positive number denotes the number of patient years needed to be treated with rivaroxaban instead of placebo to observe one additional harmful event (NNH).
CI: confidence interval; MI: CV: cardiovascular; ICH: intracranial hemorrhage; MI: myocardial infarction.
Advisory Committee Briefing Document, page 131.

major and fatal bleeding. These estimates suggest that the benefit of XARELTO® (2.5 mg po BID) outweighs the risk.

However, what is not reflected in the sponsor's analysis are minor bleeding events. While it is true that these bleeding events typically do not lead to death or irreversible harm, these events may represent the biggest problem for both patients and health care providers if rivaroxaban is approved.

To evaluate a combination of major and minor bleeding events, we could examine Clinically Significant Bleeding events, defined as the composite of TIMI major bleeding events, TIMI Minor bleeding events, or bleeding events requiring medical attention. TIMI Minor bleeding events are defined as any clinically overt sign of hemorrhage (including imaging) that was associated with a fall in hemoglobin concentration of 3 to < 5 g/dL (or, when hemoglobin concentration was not available, a fall in hematocrit of 9 to < 15%).

To evaluate lesser bleeding events, we could examine TIMI Medical Attention bleeding events, defined as events that required medical or surgical treatment or laboratory evaluation and did not meet criteria for a major or minor bleeding event.

The following calculations are based on using annualized rates of 12.02 and 7.1 for rivaroxaban 2.5 mg BID and placebo, respectively, for Clinically Significant bleeding events and on using annualized rates of 10.02 and 6.1 for rivaroxaban 2.5 mg BID and placebo, respectively, for TIMI Medical Attention bleeding events.

Under the above assumptions, rivaroxaban, 2.5 mg BID, could be expected to result in roughly 492 additional Clinically Significant bleeding events, including 392 TIMI Medical Attention bleeding events per 10,000 patient-years. From a NNT/NNH perspective, treatment of ACS patients with rivaroxaban 2.5 mg BID instead of placebo would result in 1 fewer non-bleeding CV death, MI, or ischemic stroke event per 87 patient-years, while resulting in 1 additional Clinically Significant bleeding event every 20 patient-years (or 1 additional bleeding event requiring medical attention every 26 patient-years).

While reductions in CV death still trump these bleeding events, if rivaroxaban is approved, we should expect a number of bleeding events that will require medical attention. Carefully selecting patients for rivaroxaban therapy will be necessary to mitigate these bleeding risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

XARELTO® has an existing Risk Evaluation and Mitigation Strategy (REMS)/medication guide in place for the atrial fibrillation indication. The current REMS features

1) the increased risk of thrombotic events, including stroke, if XARELTO® (15 mg and 20 mg) is discontinued without introducing an adequate alternative anticoagulant and

2) the potential for decreased efficacy of XARELTO® if not taken with the evening meal.

I recommend updating the medication guide, communication plan, and prescribing information that relate to the use of rivaroxaban in patients with ACS to highlight the following new risks identified in the review of the ATLAS ACS 2 TIMI 51 Trial:

- contraindicate XARELTO® in patients with a history of stroke or transient ischemic attack (TIA) where the point estimate for the primary efficacy endpoint is clearly adverse

- include a box warning for bleeding risk in patients ≥ 75 years of age where efficacy is uncertain and in patients weighing less than 60 kg

- include language to reflect the increased susceptibility of ACS patients to drug-induced liver injury.

1.4 Recommendations for Postmarket Requirements and Commitments

At this time, I do not think postmarket requirements are needed from a safety or effectiveness perspective.

2 Introduction and Regulatory Background

2.1 Product Information

Rivaroxaban is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor, such as Anti-thrombin III, for activity. Rivaroxaban is being co-developed through a research program between Bayer Pharma AG (Bayer) and Janssen R&D, LLC. (JR&D) (formerly Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD).

2.2 Tables of Currently Available Treatments for Proposed Indications

Rivaroxaban's proposed indication is to reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome. Currently, there are no Factor X

inhibitors approved for this indication. There are three P2Y12 inhibitors approved for this indication and warfarin.

Product	Indication
Brilinta (ticagrelor) (Approved July 20, 2011)	BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST-elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.
Effient (prasugrel) (Approved July 10, 2009)	EFFIENT is a $P2Y_{12}$ inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI as follows: • Patients with unstable angina or, non-ST-elevation myocardial infarction (NSTEMI) • Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI.
Ticlid (ticlopidine) (Approved October 31, 1991)	TICLID is indicated: • To reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. Because TICLID is associated with a risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis and aplastic anemia (see BOXED WARNING and WARNINGS), TICLID • As adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation
Coumadin (warfarin sodium) (Approved June 8, 1954)	COUMADIN is a vitamin K antagonist indicated for • Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism • Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement

	• Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction

2.3 Availability of Proposed Active Ingredient in the United States

The proposed dosage form is the rivaroxaban 2.5 mg immediate release film-coated tablets for oral administration. The 2.5 mg tablet is formulated using the same excipients as the approved 10 mg, 15 mg, and 20 mg tablets. The coating material used in the 2.5 mg tablet is Opadry Light Yellow.

Drug product for commercial supply will be manufactured at Janssen Ortho, L.L.D., Gurabo, Puerto Rico.

2.4 Important Safety Issues With Consideration to Related Drugs

The two most important safety issues with consideration to related drugs are bleeding and the possibility of liver injury.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

See Attachment 1 and Section 5.3.1.10.

2.6 Other Relevant Background Information

Table 4 summarizes the investigational new drug (IND) applications and new drug applications (NDA) for rivaroxaban at the Center for Drug Evaluation and Research at the Food and Drug Administration.

Table 4. Summary of Rivaroxaban INDs and NDAs

Application	Division	Initial Date [Approved]	Indication
IND 64892	DHP	5/30/2002	Prevention of venous thromboembolism in patients undergoing knee or hip replacement surgery
IND 075238	DCaRP	6/15/2006	Prevention of stroke and systemic embolism in patients with atrial fibrillation
IND 075,931	DCaRP	9/28/2006	Prevention of death/myocardial infarction/stroke and severe recurrent ischemia requiring revascularization in patients with acute coronary syndrome

Application	Division	Initial Date [Approved]	Indication
NDA 22,406	DHP	7/28/2008 [7/1/2011]	Prevention of venous thromboembolism in patients undergoing knee or hip replacement surgery
NDA 202,439	DCaRP	1/15/2011 [11/4/2011]	Prevention of stroke and systemic embolism in patients with atrial fibrillation
sNDA 202,439	DCaRP	12/29/2011	Reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the submission is acceptable. This electronic submission is located at

\\cdsesub1\evs[rpd\NDA202439

3.2 Compliance with Good Clinical Practices

See Section 6.1.6.1.1.

3.3 Financial Disclosures

The ATLAS ACS 2 TIMI 51 trial is the only trial providing efficacy data. The sponsor identified 8 investigators with a financial interest who contributed a total of 112 subjects to this 15,526 subject trial conducted in 44 countries at 766 sites. Given the size of this study, their participation is not thought to have influenced the outcome of this trial in any meaningful way.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No issues have been identified. Dr. Minerva Hughes of Biopharmaceutics recommends tightening the dissolution specifications to Q = (b) (4) Additionally, a new

packaging site (Anderson Packaging) has been added in this supplement. Therefore, the Office of Compliance must determine if this site is adequate for GMP production. Pre-approval inspections for the drug substance and manufacturing sites are not needed since these facilities were approved during the original NDA approval in November 2011.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Most of the toxicities identified in the non-clinical studies were either attributable to the pharmacodynamic effect of rivaroxaban or satisfactory safety margins that had been demonstrated relative to human therapeutic exposures.

Dr. Patricia Harlow identified marked increases in bleeding during parturition with rivaroxaban, compared to other anticoagulants, and embryo/fetal and perinatal toxicity to offspring as risks. She recommends that prescribing information warn women of child-bearing potential of rivaroxaban's embryo/fetal and perinatal toxicity to offspring and the high bleeding risk during labor and delivery.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

See Section 2.1.

4.4.2 Pharmacodynamics

In humans, there is dose-dependent inhibition of factor Xa activity and dose-dependent prolongation in the Neoplastin® prothrombin time (PT), activated partial thromboplastin time (aPTT), and HepTest®. Rivaroxaban also affects anti-factor Xa activity.

See Sections 7.2.2 and 7.5.4.

4.4.3 Pharmacokinetics

Rivaroxaban achieves peak plasma concentrations within 2 to 4 hours following oral administration of rivaroxaban tablets. In the dose range evaluated in ATLAS (2.5 mg BID and 5 mg BID), rivaroxaban demonstrated proportional kinetics with approximately

100% bioavailability. There was no observed food effect. The elimination half-life of rivaroxaban is about 6 to 8 hours in young healthy subjects and 11 to 13 hours in the elderly. Rivaroxaban is a substrate of the efflux transporters P-gp and BCRP. About 50% of an orally administered dose is metabolized in the liver, predominantly by CYP3A4/5. Rivaroxaban is excreted primarily in the urine (~66%). Approximately half (~36%) of the administered dose is excreted as unchanged drug.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The two trials submitted for the ACS indication are summarized in Table 5. The sponsor's tabular listing of clinical trials and studies of rivaroxaban is included in Attachment 2. Although the sponsor included study No. RIVAROXACS2001, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Escalation and Dose-Confirmation Study to Evaluate the Safety and Efficacy of Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Subjects With Acute Coronary Syndromes" (The ATLAS ACS TIMI 46 Trial (***A***nti-Xa ***T***herapy to ***L***ower Cardiovascular Events in Addition to ***A***spirin With or Without Thienopyridine Therapy in ***S***ubjects With ***A***cute ***C***oronary ***S***yndrome) in the submission, this study was designed for the purpose of Phase 3 dose selection only and contributes little to the overall assessment of the safety and effectiveness of rivaroxaban in the treatment of ACS patients. TIMI 46 will be discussed briefly in Section 6 with respect to results for Stratum 1.

Table 5. Clinical Trials Included in Submission

Study ID **EudraCT Number** **First Patient First Visit/ Completion date (day, month, year)** **Study Status**	**Country/ # of Centers**	**Phase** **Study Description/Design** **Study Population** **Primary Objective**	**Total # of Subjects**	**Study Drug; Formulation; Dose Regimen; Duration of Treatment**	**# of SubjectsTreated (by treatment group)**	**Type of Study Report/Issue Date/Document ID Number**
39039039ACS2001 (ATLAS ACS TIMI 46, Impact 11898) Eudra CT: 2006-004449-40 FPFV: 17 Nov 2006 Completion: 19 Sept 2008 Synopsis Completed	27 Countries; 297 Centers	Phase 2 Randomized, double-blind, placebo-controlled, multicenter, dose-escalation and dose-confirmation study to evaluate the safety and efficacy of rivaroxaban in combination with aspirin alone or with aspirin and a thienopyridine in subjects with acute coronary syndromes	Planned: 3600 to 3825 Screened: 3576 Randomized: 3491	Rivaroxaban 2.5 mg , 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg IR tablets (Oral) Total daily dose levels of 5 mg, 10 mg, 15 mg, and 20 mg as od or bid doses, in addition to ASA alone or ASA plus thienopyridine. The planned duration for all dose levels was 6 months.	Placebo 1153 TDD 5 mg: 307 TDD 10 mg: 1046 TDD 15 mg: 353 TDD 20 mg: 603	Full CSR Issued on 1 May 2009 Report No.: EDMS-PSDB-7122709:2.0
RIVAROXACS3001 (ATLAS ACS2 TIMI 51) Eudra CT: 2008-002708-25 FPFV: 26 Nov 2008/ Completion: 19 Sep 2011 Synopsis Completed.	44 Countries; 766 Centers	Phase 3 A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects With a Recent Acute Coronary Syndrome, in addition to ASA alone, or ASA plus a thienopyridine	Planned: 15,500 Screened: 15,932 Enrolled: 15,526 Randomized: 15,528	Rivaroxaban 2.5 mg, 5 mg (oral) 2.5 mg or 5 mg bid, in addition to ASA alone or ASA plus thienopyridine. This was an event-driven study. Mean durations were : 2.5 mg: 397 days 5 mg: 376.5 days	Placebo: 5113 Rivaroxaban 2.5 mg bid: 5115 Rivaroxaban 5 mg bid: 5110	Full CSR Issued on 18 November 2011 Report No.: EDMS-ERI-26178705:1.0
Module 5.2: Tabular Listing of Clinical Studies						

5.2 Review Strategy

The focus of this review is on results from the ATLAS ACS 2 TIMI 51 Trial. I focused on the effectiveness of rivaroxaban, bleeding events, the evaluation of net clinical benefit, and drug-induced liver injury. My cross-discipline team leader, Dr. Thomas Marciniak, focused on data quality, deaths, and discontinuations (withdrawn consent).

Although the sponsor specified that their primary analysis was modified-intent-to-treat, the analysis was an "on-treatment + 30 days" analysis. With the sponsor's late exclusion of three Indian sites (091001, 091019, and 091026) from efficacy analyses in the final statistical analysis plan (SAP) submitted on September 15, 2011, we conducted numerous sensitivity analyses including and excluding these sites, which contributed a total of 22 efficacy endpoint events, including 10 primary endpoint events and 1 non-CV death. Many of the analyses presented in this review for efficacy and safety include these sites.

5.2.1 Number of Randomized Subjects

The number of randomized subjects in each strata are summarized in Table 6. If 184 subjects from Sites 091001, 091019, and 091026 are excluded, the total number of randomized subjects is 15,526. The safety population consisted of all subjects who received at least one dose of study drug (N = 15,350).

Table 6. Number of Randomized Subjects (ATLAS)

Stratum Population	Rivaroxaban			Placebo (N=5176) n (%)	Total (N=15526) n (%)
	2.5 mg BID (N=5174) n (%)	5 mg BID (N=5176) n (%)	Combined (N=10350) n (%)		
All Strata	**5174**	**5176**	**10350**	**5176**	**15526**
All Randomized Subjects	5174 (100)	5176 (100)	10350 (100)	5176 (100)	15526 (100)
All Randomized Subjects Excluding Selected Sites*	5114 (98.8)	5115 (98.8)	10229 (98.8)	5113 (98.8)	15342 (98.8)
Safety	5115 (98.9)	5110 (98.7)	10225 (98.8)	5125 (99.0)	15350 (98.9)
Stratum 1 (ASA)	**349**	**349**	**698**	**355**	**1053**
All Randomized Subjects	349 (100)	349 (100)	698 (100)	355 (100)	1053 (100)
All Randomized Subjects Excluding Selected Sites*	349 (100)	348 (99.7)	697 (99.9)	353 (99.4)	1050 (99.7)
Safety	343 (98.3)	342 (98.0)	685 (98.1)	352 (99.2)	1037 (98.5)

Stratum Population	Rivaroxaban 2.5 mg BID (N=5174) n (%)	Rivaroxaban 5 mg BID (N=5176) n (%)	Rivaroxaban Combined (N=10350) n (%)	Placebo (N=5176) n (%)	Total (N=15526) n (%)
Stratum 2 (ASA + Thienopyridine)	**4825**	**4827**	**9652**	**4821**	**14473**
All Randomized Subjects	4825 (100)	4827 (100)	9652 (100)	4821 (100)	14473 (100)
All Randomized Subjects Excluding Selected Sites*	4765 (98.8)	4767 (98.8)	9532 (98.8)	4760 (98.7)	14292 (98.7)
Safety	4772 (98.9)	4768 (98.8)	9540 (98.8)	4773 (99.0)	14313 (98.9)

***Selected sites: 091001, 091019, 091026**
ASA: aspirin; BID: twice daily
Source: CSR, Table 5, page 85.

5.2.2 Sponsor's Descriptions of Analysis Sets for Efficacy and Safety and Event Censoring Rules

The sponsor's descriptions of the analysis sets, populations, and event censoring rules are provided in Table 7. Note that their population excludes subjects from sites 091001, 091019, and 091026.

Table 7. Analysis Sets and Event Censoring Rules

Analysis Set	Population	Event Censoring Rule
Primary Efficacy Analysis Set		
mITT	All randomized subjects excluding sites 091001, 091019, and 091026	Endpoint events that occurred from randomization up to the earlier date of 12:01 a.m. local time on 3 June 2011 [i.e., the global treatment end date], or 30 days after last dose of study drug (for subjects who discontinued study drug prematurely), or 30 days after randomization (for subjects who were randomized but never treated)
Efficacy Sensitivity Analysis		
ITT	All randomized subjects excluding sites 091001, 091019, and 091026	Endpoint events from randomization up to 12:01 a.m. local time on 3 June 2011 [i.e., the global treatment end date].

Analysis Set	Population	Event Censoring Rule
ITT-Total	All randomized subjects excluding sites 091001, 091019, and 091026	Endpoint events from randomization up to the last contact date for each subject
Treatment-Emergent Safety	Safety population (i.e., all randomized subjects who received at least one dose of study drug excluding sites 091001, 091019, and 091026)	Endpoint events from first dose up to the date of last dose of study drug plus 2 days for each subject
Per Protocol (mITT)	All randomized subjects excluding sites 091001, 091019, and 091026, and excluding subjects with any of the following major protocol deviations: • Subject received the incorrect medication kit • Subject was randomized but did not receive study drug • Subject did not withdraw as per protocol	Same censoring rules as those described above for the mITT analysis set.
Primary Safety Analysis Set		
Treatment-Emergent Safety	Safety population (i.e., all randomized subjects who received at least one dose of study drug)	All events from first dose up to the date of last dose of study drug plus 2 days for each subject
Secondary Safety Analysis Sets		
mITT Approach Safety	Safety population (i.e., all randomized subjects who received at least one dose of study drug)	All events that occurred from randomization up to the earlier date of 12:01 a.m. local time on 3 June 2011 [i.e., the global treatment end date], or 30 days after last dose of study drug (for subjects who discontinued study drug prematurely)
Safety-Observational period	Safety population (i.e., all randomized subjects who received at least one dose of study drug)	All events from first dose up to the last contact date for each subject
Per Protocol (TE-Safety)	Safety population (i.e., all randomized subjects who received at least one dose of study drug), excluding subjects with any of the following major protocol deviations • Subject received the incorrect medication kit • Subject did not withdraw as per protocol	Same censoring rule as described above for the Treatment-Emergent Safety analysis set
mITT: modified Intent-to-Treat; ITT: Intent-to-Treat **Clinical Study Report, Tables 3 and 4, pages 72-73.**		

5.3 Discussion of Individual Studies/Clinical Trials

The sponsor's global study No. RIVAROXACS3001, "A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects With a Recent Acute Coronary Syndrome" (The ATLAS ACS 2 TIMI 51 Trial (The second trial of *A*nti-Xa *T*herapy to *L*ower cardiovascular events in *A*ddition to standard therapy in *S*ubjects with *A*cute *C*oronary *S*yndrome) provides evidence for the effectiveness of rivaroxaban in the reduction of the risk of the composite endpoint of CV death, MI, or stroke in patients with acute coronary syndrome (ACS) [ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UA)].

5.3.1 The ATLAS ACS 2 TIMI 51 Trial

5.3.1.1 Study Design and Objectives

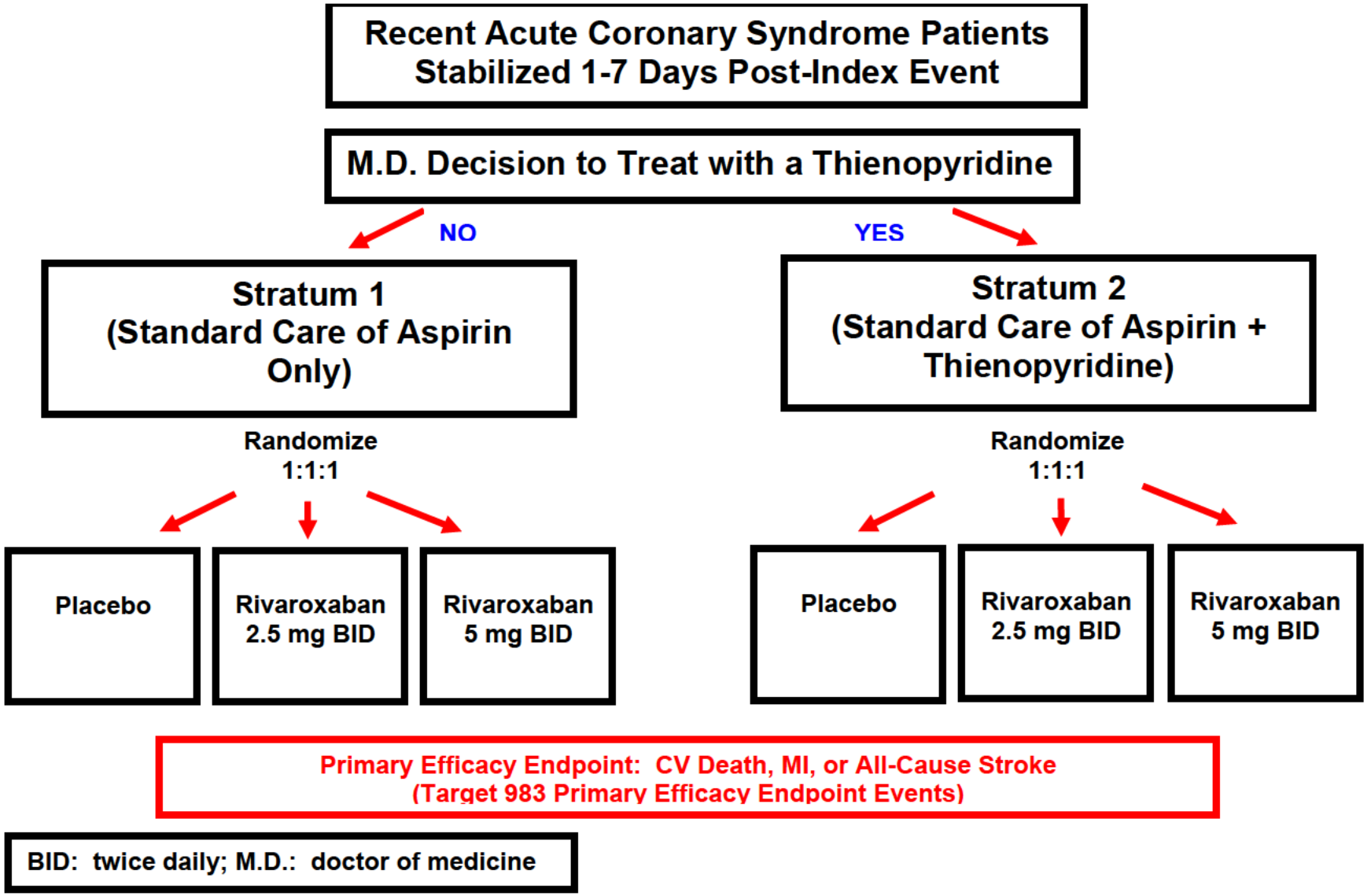
This was a randomized, double-blind, placebo-controlled, event-driven multinational study to evaluate the effectiveness and safety of rivaroxaban in subjects with a recent acute coronary syndrome (STEMI, NSTEMI, or UA) who were receiving standard care.

This study was designed as a superiority trial, and the primary objective was to determine whether rivaroxaban in addition to standard care reduced the risk of the composite of CV death, MI, or stroke in subjects with a recent ACS compared with placebo.

The study had three phases, including 1) a 6-day screening phase that could extend into Day 1 of the double-blind treatment phase (i.e., up to 7 days); 2) a double-blind treatment phase; and 3) a follow-up phase including the final end of study visit scheduled approximately 30 days after the end of treatment visit.

The study design is illustrated in Figure 1. There were two strata, Stratum 1 (aspirin) and Stratum 2 (aspirin plus thienopyridine). Randomization was stratified by the intention to use a thienopyridine. Within each stratum, subjects were randomized from 1 to 7 days after hospitalization for the index ACS event via interactive voice response system (IVRS)/interactive web response system (IWRS) in a 1:1:1 ratio to receive rivaroxaban 2.5 mg twice daily, rivaroxaban 5 mg twice daily, or placebo twice daily. Subjects were to receive low-dose aspirin (ASA) (75 -100 mg/day). The daily maintenance dosages of clopidogrel and ticlopidine were not to exceed 75 mg daily and 250 mg twice daily, respectively.

Figure 1. ATLAS Study Design



Subjects were to receive the first dose of study drug when parenteral anticoagulant therapy was discontinued and no sooner than 4 hours after the final dose of intravenous unfractionated heparin (UFH), 8 hours (changed to "2 hours" in Protocol Amendment #2) after the final dose of bivalirudin, and 12 hours after the final dose of other intravenous or subcutaneous anticoagulants (e.g., enoxaparin or fondaparinux).

Enrollment could occur as early as possible after the initial treatment for the index ACS event, including revascularization procedures, but could not occur during the first 24 hours following hospitalization.

5.3.1.2 Study Sites/Investigators

Investigators enrolled subjects at 766 sites in 44 countries. Each country was assigned to one of 6 regions as follows:

- **Asia:** China, India, Japan, Malaysia, Philippines, South Korea, Thailand
- **Eastern Europe:** Bulgaria, Croatia, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Russian Federation, Serbia, Slovakia, Ukraine
- **Western Europe:** Belgium, Denmark, France, Germany, Greece, Italy, Netherlands, Portugal, Spain, Sweden, United Kingdom
- **North America:** Canada, United States
- **South America:** Argentina, Brazil, Chile, Colombia, Mexico
- **Others:** Australia, Egypt, Israel, Morocco, New Zealand, Tunisia, Turkey

5.3.1.3 Study Duration/Dates

The study was conducted between 26 November 2008 and 19 September 2011. The first and last patient were randomized on 26 November 2008 and 22 January 2011, respectively. The global treatment end date was on 3 June 2011 at 12:01 a.m.. The final patient contact occurred on 19 September 2011. The database was locked on 24 September 2011.

5.3.1.4 Study Population (Key Inclusion/Exclusion Criteria)

Key inclusion criteria were

- Man or woman ≥ 18 years of age
- Subjects 18 to 54 years of age must also have either diabetes mellitus or a prior MI
- Subjects must currently be receiving ASA therapy (75 to 100 mg/day) alone or in combination with a thienopyridine
- Subjects must be hospitalized for ACS symptoms lasting ≥ 10 minutes within 48 hours of hospital presentation and have a diagnosis of STEMI, NSTEMI, or UA, defined as follows:

Diagnosis
STEMI Elevation of ST-segment more than 0.1 millivolt (mV) in 2 or more continuous ECG leads, or new left bundle branch block, or ST-segment depression 0.1 mV or greater in 2 of the precordial leads V1-V4 with evidence suggestive of true posterior infarction, all with elevated biomarkers of myocardial necrosis (creatinine kinase-muscle and brain isoenzyme [CK-MB] or troponin)
Non-ST-Elevation Myocardial Infarction (NSTEMI)* Transient ST-segment elevation , or ST-segment depression, or T-wave changes consistent with myocardial ischemia along with elevated biomarkers of myocardial necrosis (creatinine kinase-muscle and brain isoenzyme [CK-MB] or troponin) *Amendment 2 (August 6, 2009) revised NSTEMI entry criteria as follows: Elevated biomarkers of myocardial necrosis (creatinine kinase-muscle and brain isoenzyme [CK-MB] or troponin) plus 1 of the following: • Transient ST-segment elevation, or ST-segment depression, or T-wave changes consistent with myocardial ischemia, or • Identification of a culprit lesion at coronary angiography demonstrating recent, active intracoronary athero-thrombosis (for example, thrombus or an ulcerated plaque).
Unstable Angina (UA)** • Transient or persistent ST-segment deviation 0.1 mV or greater in 1 or more ECG leads • TIMI risk score of ≥ 3 **Amendment 2 (August 6, 2009) revised UA entry criteria to require TIMI risk score of ≥ 4, not 3.

Diagnosis

TIMI Risk Scores[18,19]	
UA/NSTEMI	
Age ≥65 years	1 point
ST deviation ≥ 0.5 mm	1 point
≥3 CAD Risk Factors (elevated cholesterol, family history of heart disease, hypertension, diabetes mellitus, smoking)	1 point
ASA in last 7 days	1 point
≥2 anginal events ≤24 hours	1 point
Prior CAD (cath stenosis >50%)	1 point
Elevated CK-MB or troponin	1 point
STEMI	
Age ≥75 years	3 points
Age 56-74 years	2 points
Diabetes mellitus, hypertension, or angina	1 point
Systolic blood pressure <100 mmHg	3 points
Heart rate >100 bpm	2 points
Killip Class II-IV	2 points
Weight <67 kg	1 point
Anterior STE or LBBB	1 point
Time to treatment >4 hours	1 point

Key exclusion criteria were

- Bleeding risk (active internal bleeding, platelet count < 90,000/µL, history of intracranial hemorrhage, gastrointestinal bleeding within 12 months, abciximab within 8 hours)
- Severe concomitant diseases (cardiogenic shock; refractory ventricular arrhythmias; creatinine clearance (CrCl) < 30 mL/min; known significant liver disease; prior ischemic stroke or TIA (excluded from Stratum 2 only); anemia; HIV
- Known aspirin allergy; systemic treatment with strong CYP3A4 and P-gp inhibitors; atrial fibrillation (except for subjects younger than 60 years of age who have no echocardiographic evidence of cardiopulmonary disease and had a single episode only more than 2 years ago)

5.3.1.5 Treatments

In each stratum, subjects were randomized in a 1:1:1 ratio to the following treatment groups:

- Rivaroxaban 2.5 mg twice daily
- Rivaroxaban 5 mg twice daily
- Placebo twice daily

All study drugs were to be taken once in the morning and once in the evening, approximately 12 hours apart, at about the same time each day, irrespective of meals.

5.3.1.6 Procedures

Study procedures are summarized in Table 8.

5.3.1.7 Endpoints

5.3.1.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the composite of cardiovascular (CV) death, myocardial infarction (MI), or stroke.

5.3.1.7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints included

- The composite of all cause death, MI, or stroke
- Net clinical outcome, defined as the composite of CV death, MI, ischemic stroke, or TIMI major bleeding event not associated with CABG surgery
- The composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization (SRIR)
- The composite of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalization (SRIH)

5.3.1.7.3 Exploratory Efficacy Endpoints

The EuroQol (EQ-5D), a patient-reported outcome measure, was used to assess the current health state of the subject. The EQ-5D includes 5 questions with respect to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These descriptive questions would be used to generate utility scores (0 to -1). The visual analog scale (VAS) would provide a graphical representation ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

5.3.1.7.4 Safety Endpoints

The primary safety endpoint was TIMI Major non-CABG surgery-related bleeding events in the treatment-emergent safety analysis set, defined as all subjects who received at least one dose of study drug and experienced endpoint events between the first study drug administration and 2 days after the last study drug administration, inclusive.

Table 8. Time and Events Schedule (ATLAS)

	Screening[a]	Treatment Phase[b]											Follow-Up	
		Baseline	Double-Blind Treatment										Early Discontinuation Contact (30 days after study drug discontinuation and then every 12 wks)[e]	End-of-Study Visit[f]
Day(s)/Weeks (wks)	Days –6 to –1	Day 1[a]	4 wks	12 wks	24 wks	36 wks	48 wks	60 wks	72 wks	84 wks	96 wks	Every 12 wks[c],	EOT/Early Withdrawal[d]	
Screening Procedures														
Informed consent	X													
Inclusion/exclusion criteria	X													
Medical history	X													
Body weight, waist circumference, and height	X													
Preplanned surgical procedures assessed	X													
Urine pregnancy test[g]	X												X	
Record current medications (identity only)	X													
Efficacy/Safety Procedures														
Hematology[h]	X[i]	X[i]	X											
Clinical chemistry[h]	X[i]	X[i]	X											
ALT and total bilirubin only				X	X								X[j]	
Clinical status review: record endpoint events[k], adverse events, adverse events leading to discontinuation, adverse events of special interest,[l] MRU data,[m] and record concomitant medications (identity only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Economic Evaluations														
EuroQol (EQ-5D)[n]		X	X		X		X		X		X		X		
Study Drug Administration														
Randomization		X												
Study drug administration[o,p,q]		X	X	X	X	X	X	X	X	X	X	X			
Dispense study drug as needed[r]		X	X	X	X	X	X	X	X	X	X	X			
Rivaroxaban or placebo accountability[s]			X	X	X	X	X	X	X	X	X	X	X		

EOT=end-of-treatment, ALT=alanine aminotransferase.

[a] Screening evaluations will be performed up to 7 calendar days after the subject has been hospitalized for the index ACS event (i.e., during the 6-day screening phase [Days –6 to –1] plus Day 1 of the double-blind treatment phase, as long at the screening evaluations are completed before randomization on Day 1). All baseline evaluations must be completed before randomization. Both screening and baseline evaluations may occur on the day of randomization (defined as Day 1). If the subject develops symptoms of ACS while hospitalized for a condition other than ACS, then this ACS event will be counted as index event and will trigger the screening time line not the date of initial hospitalization.

[b] The baseline visit (Day 1) must occur on Day 1. Week 4 visit should be accomplished within -4 to +2 days of the target day, and Week 12 visit should be accomplished within ±4 days of the target day. All other visits should be accomplished within ±6 days of the target day.

[c] Until the pre-specified number of adjudicated primary efficacy endpoint events has been reached.

[d] To be conducted in all subjects once the specified number of primary efficacy endpoints is reached. For those subjects who discontinue treatment before the end of the double-blind treatment, the subject should complete the end-of-treatment/early withdrawal procedures

[e] Subjects who discontinue study drug treatment prematurely will be contacted 30 days later, and will continue to be contacted every 12 weeks after the follow-up visit until the end of the study.

[f] Once the pre-specified number of primary efficacy endpoints is reached, all subjects currently receiving blinded study drug, at all study centers, should complete the end-of-treatment early/withdrawal visit, and should complete the final end-of-study visit 30 days later to assess efficacy and safety data. Those subjects who discontinue study drug early should also complete the final end-of-study visit with a minimum of 30 days posttreatment follow-up.

[g] To be performed on all women of childbearing potential.

[h] Hematology and clinical chemistry analytes are described in Section 9.5, Safety Evaluations.

[i] Subjects may be screened and randomized using either local laboratory or central laboratory results for the inclusion and exclusion clinical laboratory parameters. Screening blood samples should be obtained at least 24 hours after hospital presentation and after the subject has stabilized. All screening clinical laboratory results must be completed and reviewed before randomization. Screening laboratory results obtained locally will only be recorded on the case report form (CRF) if the baseline laboratory results are exclusionary. All randomized subjects must have samples sent to the central laboratory before randomization.

[j] Subjects who are withdrawing before Week 24 visit.

[k] In subjects suspected of ischemic, hemorrhagic or unknown stroke, a follow-up neurologic exam will take place as well as an assessment of the modified Rankin disability scale score should be utilized. For any stroke occurring within the first 4 weeks, this will occur at the Week 12 visit. For a stroke accruing after Week 4, follow-up neurologic assessment should occur approximately 8 to 12 weeks following the event.

[l] Adverse events of special interest (see Section 9.5, Safety Evaluations) and any previously reported and unresolved adverse events will be assessed.

[m] MRU data will not be collected at baseline/Day 1.

[n] To be performed in a subset of subjects (see Section 3.2, Study Design [subsection EuroQol] and Section 9.6.1, EuroQol).

[o] Subjects will self administer study drug (rivaroxaban 2.5 mg, rivaroxaban 5 mg, or placebo) orally twice daily once in the morning and once in the evening (approximately 12 hours apart), at approximately the same times each day. All subjects will also receive standard care as prescribed by their managing physician.

[p] Subjects who experience any of the primary or secondary efficacy endpoint events (except for death and hemorrhagic stroke) will continue to receive blinded study drug and complete all assessments at all scheduled visits, if possible. Subjects who discontinue study drug treatment prematurely will complete the end-of-treatment/early withdrawal procedures, and will be contacted 30 days and every 12 weeks until the study ends.

[q] Once the required number of adjudicated primary efficacy endpoint events has been reached, subjects still receiving study drug will be scheduled to complete the end-of–treatment/early withdrawal procedures.

[r] Study drug will be dispensed on Day 1 after randomization, 4 weeks, 12 weeks, and then every 12 weeks thereafter until the required number of efficacy endpoint events is reached.

[s] Review of the subject's compliance with taking study drug.

(Protocol Amendment 2, dated August 6, 2009, pages 30-32)

Other bleeding endpoints included

- TIMI major and/or TIMI minor
- Clinically significant bleeding, i.e., the composite of TIMI Major, TIMI Minor, or Bleeding Events Requiring Medical Attention
- Bleeding Events according to the ISTH criteria
- Bleeding Events according to the GUSTO criteria
- All bleeding events according to TIMI classification

5.3.1.7.5 Adverse Events of Special Interest

Adverse events of special interest were defined as

- Any liver-related adverse event, including ALT > 3 times the ULN (and normal baseline) with confirmation by retesting (within 5 days)
- Any bleeding event that did not meet serious adverse event criteria
- Any event occurring within 30 days before a permanent discontinuation

5.3.1.8 Endpoint Definitions

The Clinical Events Committee (CEC) adjudicated all efficacy endpoints using the following definitions.

5.3.1.8.1 Efficacy Endpoint Definitions

- **Death**
  Death was classified in 2 primary categories, cardiovascular or noncardiovascular, and also in 2 secondary categories, coronary heart disease (CHD) related or non-CHD related. All deaths were assumed cardiovascular in nature unless a noncardiovascular cause could be clearly shown.

- **Myocardial Infarction**
  All myocardial infarctions were counted as events whether they represented the reason for the hospitalization or occurred during a hospitalization. In addition, they were counted as events whether they occurred spontaneously or as the direct consequences of an investigation/procedure or operation.

  In order to meet the criteria as an endpoint, an MI had to be distinct from the qualifying event (i.e., re-infarction for a subject who qualified for the study based on recent MI).

  The definition of MI as an endpoint took into account whether a subject had a recent MI or had undergone revascularization with PCI or CABG surgery. In cases where both cardiac troponin and CK-MB were available (collected at similar time points) and were discordant, clinical judgment was used to apply the most relevant

biomarker data. The definitions of MI were as follows for the 4 clinical settings in which it could occur:

A. For patients with no recent revascularization, criteria (1) and (2) or criterion (3) or criterion (4) must have been met:

1. Typical cardiac biomarker rise and fall with the following degrees of elevation accepted as biochemical evidence of myocardial necrosis:

   a. Troponin T or I: maximal concentration greater than the MI decision limit
   b. CK-MB: maximal concentration greater than the ULN;

   AND

2. At least 1 of the following additional supportive criteria:

   a. Ischemic discomfort at rest lasting ≥ 10 minutes; or
   b. ECG changes indicative of ischemia (ST elevation ≥ 0.1 mV or ST depression ≥ 0.05 mV, or new T-wave inversions)

   OR

3. Development of new, abnormal Q waves (≥ 30 msec in duration and ≥ 1 mm in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads; or increased R amplitude in V1-V3 consistent with posterior infarction;

   OR

4. Pathologic findings of an acute MI

B. For patients with no recent revascularization in who biomarkers from a qualifying (or recent) MI remained elevated, criteria (1) and (2), or criterion (3), or criterion (4), or criterion (5) must have been met:

1. Cardiac biomarker re-elevation defined as:

   a. Increase by at least 20% of the previous value; and
   b. Documentation that the biomarker assayed was decreasing prior to the suspected new MI;

   AND

2. At least 1 of the following additional supportive criteria:

   a. Ischemic discomfort at rest lasting ≥ 10 minutes; or
   b. ECG changes indicative of ischemia (ST elevation ≥ 0.1 mV or ST depression ≥ 0.05 mV, or new T-wave inversions);

   OR

3. Development of new, abnormal Q waves (≥ 30 msec in duration and ≥ 1 mV in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads; or increased R amplitude in V1-V3 consistent with posterior infarction;

4. New elevation of ST-segments ≥ 0.1 mV in ≥ 2 contiguous precordial or adjacent limb leads

   AND

   a. Ischemic discomfort at rest lasting ≥ 20 minutes; or
   b. Ischemia-mediated new hemodynamic decompensation requiring pharmacologic or mechanical support; or
   c. Angiographic evidence of acute coronary occlusion

5. Pathologic findings of an acute MI

C. Within 24 hours after PCI (or felt to be clinically related to a PCI) a patient must have had EITHER:

1. CK-MB > 3 x ULN and, if the pre-PCI CK-MB was > ULN, both an increase by at least 20% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

   OR

2. Pathologic findings of an acute MI

Note: Symptoms were not required.

D. Within 24 hours after CABG (or felt to be clinically related to CABG), a patient must have had criteria (1) and (2), or criterion (3), or criterion (4):

1. CK-MB > 5 x ULN and, if the pre-CABG CK-MB was above ULN, both an increase by at least 20% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

AND

2. At least one of the following supportive criteria:

    a. Development of new, abnormal Q waves (≥ 30 msec in duration and ≥ 1 mm in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads; or increased` R amplitude in V1-V3 consistent with posterior infarction, or
    b. Angiographically documented new graft or native coronary occlusion, or
    c. Imaging evidence of new loss of myocardium

OR

3. CK-MB > 10 x ULN and, if the pre-CABG CK-MB was above ULN, both an increase by at least 20% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

4. Pathologic findings of an acute MI

Note: Symptoms were not required.

Note: If cardiac troponin measurements were the only cardiac biomarker data available, they might be used by the CEC, along with the ECG and clinical scenario, in the adjudication of suspected MI after revascularization (PCI or CABG).

If the subject was classified as having a MI, then the clinical classification of the type of MI was adjudicated (based on criteria from the Universal Definition of MI, Thygesen et al. 2007).

MI Type	Description
Type 1	Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as a plaque erosion and/or rupture, fissuring, or dissection
Type 2	Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
Type 4a	Myocardial infarction associated with PCI.

MI Type	Description
Type 4b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with CABG

- **Stroke**
  Stroke was defined as a new, sudden focal neurological deficit resulting from a presumed cerebrovascular cause that was not reversible or resulted in death within 24 hours and was not due to a readily identifiable cause, such as a tumor or seizure. Stroke would be subclassified into 1 of the following 4 groups:

  - Ischemic Infarction: Stroke without focal collections of intraparenchymal blood on a brain imaging scan

  - Ischemic infarction with hemorrhagic conversion: Infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage. This was further divided into symptomatic and asymptomatic hemorrhagic conversion. Cases of microhemorrhage were also categorized. (Per CEC Charter 9/15/2011, "Microhemorhages evident on MRI, whether in the cortex or deep brain structures, were not considered to be consistent with a hemorrhagic conversion endpoint.")

  - Primary hemorrhagic: an intraparenchymal hemorrhage, subdural, or epidural hematoma

    - Intraparenchymal hemorrhage: Stroke with focal collections of intraparenchymal blood seen on a brain image (computed tomography [CT] or magnetic resonance imaging [MRI]) or a postmortem examination, not felt to represent hemorrhagic conversion. Subarachnoid hemorrhage should be included in this category. (Per CEC Charter 9/15/2011, "Microhemorrhages discovered on brain imaging in the absence of associated symptoms or not in the relevant part of the brain to account for the symptoms in the absence of other brain lesions were not considered to be a primary intraparenchymal hemorrhage endpoint.")

    - Subdural hematoma: density representing fluid collection in subdural space on brain images or blood in the subdural space on autopsy

    - Epidural hematoma: density representing fluid collection in epidural space on brain images or blood in the epidural space on autopsy.

  - Uncertain: any stroke without brain imaging (e.g., CT or MRI), surgical exploration, autopsy, other documentation of type, or if tests were inconclusive.

The following events were not counted as a primary stroke endpoint: Subdural and epidural bleeding events and ischemic cerebrovascular events with symptoms lasting less than 24 hours (these would be considered TIAs).

- **Severe Recurrent Ischemia**
  Severe recurrent ischemia was defined as ischemic discomfort or equivalent meeting the following criteria:

  - Lasting 10 minutes at rest, or repeated episodes at rest lasting ≥ 5 minutes, or an accelerating pattern of ischemic discomfort (episodes that were more frequent, severe, longer in duration, and precipitated by minimal exertion), considered to be myocardial ischemia upon final diagnosis

  - At least one of the following additional criteria for coronary artery disease and/or ischemia:

    - New and/or dynamic ST-depression > 0.05 mV, ST-elevation > 0.1 mV, or symmetric T wave inversion > 0.2 mV on a resting ECG

    - Definite evidence of ischemia on stress echocardiography, myocardial scintigraphy (e.g., an area of clear reversible ischemia), or ECG-only stress test (e.g., significant dynamic ST shift, horizontal or downsloping)

    - Angiographic evidence of epicardial coronary artery stenosis of > 70% diameter reduction and/or evidence for intraluminal arterial thrombus

- **Severe Recurrent Ischemia Requiring Revascularization**
  Severe recurrent ischemia as defined above prompting coronary revascularization during an unscheduled visit to a healthcare facility or during an unplanned (or prolonged) hospitalization for these symptoms. Attempted revascularization procedures, even if not successful, were counted. Potential ischemic events meeting the criteria for myocardial infarction were not adjudicated as urgent coronary revascularization.

- **Severe Recurrent Ischemia Requiring Hospitalization**
  Severe recurrent ischemia as defined above prompting hospitalization (including an overnight stay on an inpatient unit) within 48 hours of the most recent symptoms. If subjects were admitted with suspected myocardial ischemia, and subsequent testing revealed a noncardiac or nonischemic etiology, this was not recorded as meeting this endpoint. Potential ischemic events meeting the criteria for myocardial infarction were not adjudicated as ischemia requiring hospitalization.

- **Stent Thrombosis** (definition included in CEC Charter only)

  Per the Statistical Analysis Plan, Amendment 1 (October 4, 2010), stent thrombosis was "not a formal study endpoint in the study protocol (even though it was adjudicated)."

  Stent thrombosis was defined based on the Academic Research Consortium (ARC) definitions (TCT 2006).

  1. **Definite/Confirmed: Angiographic stent thrombosis (1.1 or 1.2) AND 1.3:**

     1.1 TIMI flow grade 0 with occlusion originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus (*) as reported by the operator.

     1.2 TIMI flow grade 1, 2, or 3 originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus (*).

     1.3 At least one of the following criteria (within 48 h):

     1. New onset of ischemic symptoms at rest (typical chest pain > 20 min)
     2. New ischemic ECG changes suggestive of acute ischemia
     3. Typical rise and fall in cardiac biomarkers.

     *Note: The incidental angiographic documentation of silent stent occlusion in the absence of clinical signs or symptoms was not considered a confirmed stent thrombosis.

  2. **Probable:** Any unexplained death within the first 30 days; irrespective of the time after the index procedure, any myocardial infarction (MI) which was related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

  3. **Possible:** Any unexplained death from 30 days following intracoronary stenting until end of trial follow-up.

5.3.1.8.2 Bleeding Definitions

The CEC adjudicated bleeding events using three bleeding classifications including TIMI, International Society on Thrombosis and Haemostasis (ISTH), and GUSTO defined below.

The primary safety endpoint was TIMI Major Non-CABG Surgery-Related bleeding events.

5.3.1.8.2.1 TIMI Bleeding Event Classification Scale

TIMI bleeding was classified as follows:

- **TIMI Major Bleeding Event**

  - **Non-CABG-Related**
    A Non-CABG-Related TIMI major bleeding event was defined as
    - Any symptomatic intracranial hemorrhage, or
    - Clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of ≥ 5 g/dL (or when the hemoglobin concentration was not available, an absolute drop in hematocrit of ≥ 15%)

  - **CABG-Related*** (included in CEC Charter only)
    A CABG-Related TIMI major bleeding event was defined as
    - CABG-related fatal bleeding (i.e., bleeding that directly resulted in death)
    - Perioperative intracranial bleeding
    - Reoperation following closure of the sternotomy incision to control bleeding
    - Transfusion of greater than or equal to 5 units of whole blood or packed red blood cells (PRBCs) within a 48 hour period (cell saver transfusion was not counted in calculations of blood products), or chest tube output > 2 L within a 24 hour period.

    *Per the CEC Charter, for the TIMI scale, bleeding that occurred in the setting of CABG was classified as a CABG-Related TIMI major bleed, or as not a CABG-related TIMI Major Bleed. Events associated with CABG, were not classified as TIMI minor bleeding or bleeding requiring medical attention.

- **TIMI Minor Bleeding Event**
  A TIMI minor bleeding event was defined as any clinically overt sign of hemorrhage (including imaging) that was associated with a fall in hemoglobin concentration of 3 to < 5 g/dL (or, when hemoglobin concentration was not available, a fall in hematocrit of 9 to < 15%).

- **Bleeding Events Requiring Medical Attention**
  A bleeding event requiring medical attention was defined as any bleeding event that required medical treatment, surgical treatment, or laboratory evaluation and did not meet criteria for a major or minor bleeding event, as defined above.

  Examples of medical treatment, surgical treatment, or laboratory evaluation included the following: laboratory evaluation; CT or MRI; nasal packing; endoscopy; colonoscopy; cystoscopy; bronchoscopy; compression; ultrasound-guided closure of an aneurysm; coil embolization; pericardiocentesis; inotropin support; reducing or removing antiplatelet therapies; stopping the study medication (either temporarily or permanently); surgery.

- **Insignificant Bleeding Events**
  An insignificant bleeding event was defined as a reported blood loss or bleeding event episode not meeting any of the above criteria

- **Clinically Significant Bleeding Events** (included in protocol only)
  The composite endpoint of TIMI major bleeding event, TIMI minor bleeding event, or bleeding event requiring medical attention was considered clinically significant for the TIMI scale.

- **Life-Threatening Bleeding Events** (definition included in CEC Charter only)
  TIMI bleeding events were further classified as life-threatening if any of the following features were present:
  - Fatal;
  - Led to hypotension requiring treatment with intravenous inotropic agents;
  - Required surgical intervention for ongoing bleeding
  - Necessitated the transfusion of 4 or more units of blood (whole blood or packed red blood cells) over a 48-hour period;
  - Symptomatic intracranial hemorrhage

5.3.1.8.2.2 International Society on Thrombosis and Haemostasis (ISTH) Event Classification Scale

International Society on Thrombosis and Haemostasis (ISTH) bleeding was classified as follows:

- **ISTH Major Bleeding Event**
  A major bleeding event was defined using ISTH criteria as clinically overt bleeding that was associated with
  - A fall in hemoglobin of 2 g/dL or more, or
  - A transfusion of 2 or more units of packed red blood cells or whole blood, or

- A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome

- **Clinically Relevant Nonmajor Bleeding Events**

  A clinically-relevant nonmajor bleeding event was defined as an overt bleeding event not meeting the criteria for a major bleeding event, but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life.

  Examples of nonmajor clinically relevant bleeding events were:
  - Unscheduled contact (visit or telephone call) with a physician (included in CEC Charter only)
  - Study drug temporarily discontinued
  - Study drug permanently discontinued
  - Epistaxis if it lasted for more than 5 minutes, if it was repetitive (i.e., 2 or more episodes of true bleeding, i.e., no spots on a handkerchief, within 24 hours), or led to an intervention (packing, electrocautery, etc.)
  - Gingival bleeding if it occurred spontaneously (i.e., unrelated to tooth brushing or eating), or if it lasted for more than 5 minutes
  - Hematuria if it was macroscopic, and either spontaneous or lasted for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract
  - Macroscopic gastrointestinal hemorrhage: at least 1 episode of melena or hematemesis, if clinically apparent
  - Rectal blood loss, if more than a few spots
  - Hemoptysis, if more than a few speckles in the sputum, or
  - Intramuscular hematoma
  - Subcutaneous hematoma if the size was larger than 25 cm^2 or larger than 100 cm^2 if provoked
  - Multiple source bleeding events
  - Surgery (CEC Charter only)

- **Minimal Bleeding Events**

  All other overt bleeding events not meeting the criteria for major or clinically-relevant nonmajor bleeding events were classified as minimal bleeding events.

5.3.1.8.2.3 GUSTO Bleeding Event Classification Scale

There were three classes of GUSTO bleeding as follows:

- **Severe or Life Threatening**
  Severe or life-threatening was defined as either an intracranial hemorrhage or bleeding that caused hemodynamic compromise and required intervention

  CEC definition was for Severe Bleeding Event as follows: "clinically overt bleeding that was fatal, intracranial, or that caused hemodynamic compromise requiring intervention (e.g., systolic blood pressure < 90 mm Hg that required blood or fluid replacement, or vasopressor/inotropic support,* or surgical intervention)

  *Need for vasopressor/inotropic support for hemodynamic compromise, even if blood pressure was > 90 mm Hg with treatment."

- **Moderate**
  Moderate bleeding was defined as bleeding that required blood transfusion but did not result in hemodynamic compromise

- **Mild**
  Mild bleeding was defined as bleeding that did not meet criteria for either severe or moderate bleeding

5.3.1.9 Safety Procedures

5.3.1.9.1 Monitoring and Evaluation of Liver Function

Per the protocol, any subject with an ALT > 3 times the upper limit of normal (ULN) (either local or central laboratory) was to be retested as soon as possible within 5 days. Retesting and subsequent testing was to include ALT, AST, total and direct bilirubin, and alkaline phosphatase. Study drug could be continued during this time. If the repeat ALT value was lower or not increased by more than 0.5 times the ULN (≤ 3.5 times the ULN), weekly monitoring of these laboratory parameters would be performed until the ALT was < 3 times the ULN, at which time testing was continued every 2 weeks until the ALT was less than the ULN or returned to baseline (if the baseline was elevated). If elevated ALT values between the ULN and 3x ULN persisted for more than 2 months, testing frequency could be reduced to monthly, but ALT was to be less than the ULN or at the subject's baseline on at least 2 consecutive occasions prior to discontinuation of liver monitoring. If the repeat ALT was higher (> 0.5 times the ULN), laboratory parameters were to be measured every ≤ 3 days, until ALT was < 3 times the ULN. If values remained elevated, stopping rules were to be implemented.

The following abnormalities were to be reported as serious adverse events:

- Clinical manifestation of liver injury (e.g., jaundice, dark urine, ascites)
- ALT > 5 times the ULN
- Persistent ALT elevation of > 3 times the ULN for 4 weeks or longer, except for subjects with ALT > 3 times the ULN at baseline
- ALT > 3 times the ULN and an increase in ALT by > 1 ULN-Unit within 1 week
- ALT > 3 times the ULN and a total bilirubin > 2 times the ULN
- All discontinuations due to elevated LFTs

Greater elevations of ALT levels were also to be recorded as adverse events.

Subjects who had an ALT > 3 times the ULN and a total bilirubin > 2 times the ULN, would have additional laboratory testing conducted, including but not limited to testing for viral hepatitis, cytomegalovirus, Epstein-Barr virus, HIV (with written consent), ferrritin levels, iron, iron binding capacity, antinuclear antibody (ANA), and smooth muscle antibodies.

5.3.1.9.2 Discontinuation Criteria

A subject was to be discontinued from the study if

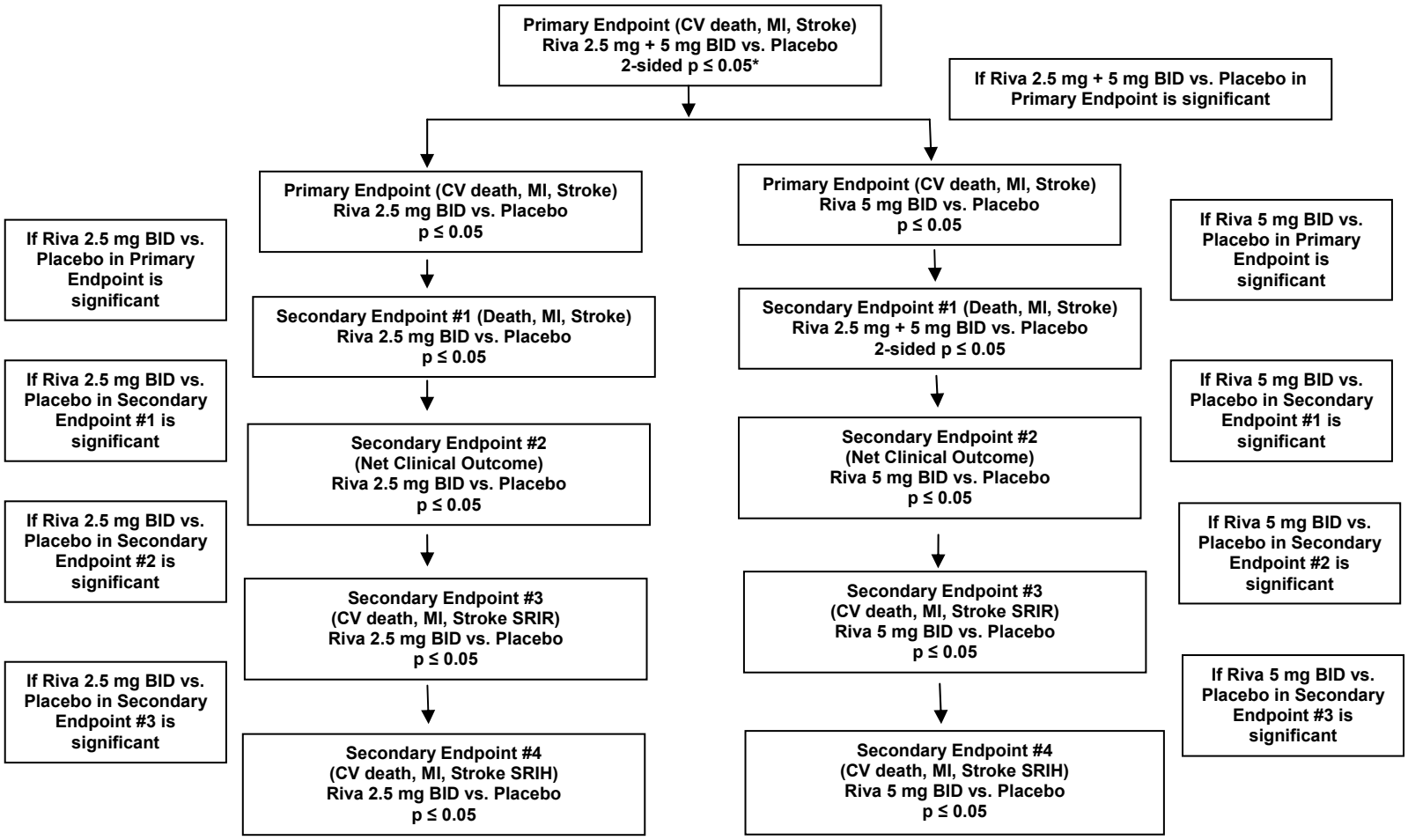
- The investigator believed that for safety reasons (i.e., adverse event) it was in the best interest of the subject to stop study drug
- The subject became pregnant
- The subject was inadvertently randomized and in the opinion of the investigator, after consultation with the study sponsor representative/designee, continuation of study drug was not advisable
- The subject requested to discontinue study drug permanently
- The subject had an ALT value ≥ 5 times the ULN with a normal baseline confirmed within 5 days
- The subject had ALT > 3 times the ULN and total bilirubin > 2 times the ULN
- The subject had intracranial bleeding
- The subject had bleeding into a critical organ, including intraocular bleeding

5.3.1.10 Statistical Analysis Plan

The original statistical analysis plan (SAP) was submitted on June 19, 2009 (SDN 871) and Amendments #1 and #2 were submitted on October 5, 2010 (SDN 1467) and September 15, 2011 (SDN 1701), respectively.

For the primary endpoint, these SAPs described two simultaneous evaluation strategies, selected on the basis of different regulatory requirements. The sponsor's testing procedure is illustrated in Figure 2. The primary evaluation strategy combined data across both strata (i.e., All Strata). The second evaluation strategy, recommended by FDA, combined data across both dose groups in Stratum 2 subjects only.

Figure 2. Diagram of Testing Procedure (ATLAS)



Key for Figure 2: BID: twice daily; CV: cardiovascular; MI: myocardial infarction; SRIH: severe recurrent ischemia requiring hospitalization; SRIR: severe recurrent ischemia requiring revascularization.

If a dose group met superiority for the primary efficacy endpoint, secondary efficacy endpoints for the same dose group could be tested sequentially using the same 2-sided significance level of 0.050. Subsequent secondary endpoints could be tested only for the doses that were statistically significant for the previous endpoint. If a dose group was not found to be statistically significant, while testing could continue, significance could not be claimed. This hierarchical testing strategy was identical for Stratum 2.

On July 15, 2009, the Division sent the sponsor a statistical advice letter with the following comments and recommendations:

1. At the end of Phase 2 meeting on June 30, 2008, the Division expressed concern about Stratum 1 (aspirin) and its lack of clinical relevance to the U.S. ACS population, since the standard of care was to place these patients on aspirin plus a thienopyridine. Therefore, Biometrics recommended that the sponsor clearly state in the SAP that both testing strategies (All Strata; Stratum 2) would need to be successful in order to make the claim for Stratum 2 (aspirin + thienopyridine).

2. The sponsor was encouraged not to spend alpha on the proposed secondary endpoints because they were similar to the primary endpoint. The likelihood of getting a claim on the proposed secondary endpoints was low.

3. If the sponsor insisted on testing the secondary endpoints, the proposed testing procedure might not have control on the family-wise type I error rate which could be as large as 10% in some scenarios.

The sponsor did not address these concerns in the subsequent two Amendments to the SAP.

Throughout the entire ACS program, there was no clear agreement between the sponsor and FDA with respect to what constituted the primary efficacy analysis set (? All Strata or Stratum 2), and inclusion/exclusion of the three Indian sites (091001, 091019, and 091026).

The primary efficacy endpoint was the composite of CV death, MI, or stroke. The sponsor's proposed primary analysis was modified Intent-to-Treat (mITT) with a 30-day censoring rule. What the sponsor called a mITT analysis was actually an "on-treatment plus 30 days analysis." Comparisons between treatment groups were performed using a Cox regression analysis with treatment in the model.

The FDA Biometrics team consistently recommended an ITT analysis for the primary analysis.

The sponsor proposed the following sensitivity analyses for efficacy: 1) Intent-to-Treat (ITT) Observational Period; 2) Treatment-Emergent Observational Period; and 3) ITT-

Total Observational Period. These analysis sets are defined in Table 9. The final SAP, submitted 9 days prior to data lock, excluded Sites 091001, 091019, and 091026 from all efficacy analyses. FDA Biometrics' review of this SAP indicated that making late changes to the SAP were problematic and could impact the interpretation of the study results; therefore, sensitivity analyses including/excluding these sites should be conducted.

Table 9. Efficacy Analysis Sets (ATLAS)

Efficacy Analysis Sets	**Randomized Subjects (excluding Sites 091001, 091019, and 091026)**		
	Randomized but not treated	**Early discontinuation** (stop treatment prior to global treatment end date[§])	**Treated per protocol** (stop treatment on or after global treatment end date[§])
Primary			
mITT Observational Period	All data from randomization up to the earlier date of 30 days after randomization and the global treatment end date	All data from randomization up to the earlier date of 30 days after last dose and the global treatment end date	All data from randomization up to the global treatment end date
Sensitivity Analyses			
ITT Observational Period	All data from randomization up to the global treatment end date	All data from randomization up to the global treatment end date	All data from randomization up to the global treatment end date
Treatment-Emergent Observational Period	Not applicable	All data from first dose up to the last dose date plus 2 days for each subject	All data from first dose up to the last dose date plus 2 days for each subject
ITT-Total Observational Period	All data from randomization up to the last contact date for each subject	All data from randomization up to the last contact date for each subject	All data from randomization up to the last contact date for each subject
[§]The global treatment end date for ATLAS was June 3, 2011 at 12:01 a.m. local time. Statistical Analysis Plan Amendment #2 dated September 12, 2011, Table 1, page 16.			

For safety, the primary analysis was the Treatment-Emergent Safety Observational Period. Sensitivity analyses included the mITT Approach Safety Observational Period and the Safety Observational Period, as defined in Table 10.

Table 10. Safety Analysis Sets

Safety Analysis Sets	Randomized Subjects who take at least one dose of study drug (i.e. Treated Subjects)	
	Early discontinuation (stop treatment prior to global treatment end date[§])	Treated per protocol (stop treatment on or after global treatment end date[§])
Primary:		
Treatment-emergent safety observational period	All data from first dose up to the last dose date plus 2 days for each subject	All data from first dose up to the last dose date plus 2 days for each subject
Sensitivity Analyses:		
mITT approach safety observational period (Align with efficacy)	All data from first dose up to the earlier date of 30 days after last dose and global treatment end date	All data from first dose up to the global treatment end date
Safety observational period (Post Baseline) (Includes all events)	All data from first dose up to the last contact date for each subject	All data from first dose up to the last contact date for each subject
[§]The global treatment end date for ATLAS was June 3, 2011 at 12:01 a.m. local time. Statistical Analysis Plan Amendment #2 dated September 12, 2011, Table 2, page 17.		

5.3.1.10.1 Treatment Comparisons

A stratified (stratified by the intention to use a thienopyridine [yes or no]) or unstratified (stratum 2 alone) log-rank test was the primary analysis for hypothesis testing on pooled rivaroxaban versus placebo. A similar stratified log rank test using the same stratum variable (or without stratum if for stratum 2 alone) would be performed for individual dose comparisons, i.e., rivaroxaban 2.5 mg BID vs. placebo and rivaroxaban 5 mg BID vs. placebo.

A stratified (stratified by the intention to use a thienopyridine [yes or no]) or unstratified (stratum 2 alone) Cox proportional regression model was used with treatment group (rivaroxaban vs. placebo) as the covariate to provide a point estimate and 95% confidence interval for the treatment effect of the relative risk reduction. A similar stratified Cox model using the same stratum variable (or without stratum if for stratum 2 alone) was used for individual dose comparisons.

5.3.1.10.2 Power Calculation

This was an event-driven trial. A total of 983 primary efficacy endpoint events would have approximately 96% power to detect a 22.5% relative reduction (i.e., hazard ratio=0.775) between pooled doses of rivaroxaban and placebo arms pooled across Stratum 1 and 2, with a 2-sided type I error rate of 0.05, based on a log-rank statistic with 2:1 allocation (rivaroxaban:placebo). The 983 events were estimated based on the sum of the events required at approximately 90% power in each stratum, to detect a 35% relative risk reduction in Stratum 1 (255 primary efficacy endpoint events needed) and a 22.5% relative reduction in Stratum 2 (728 primary efficacy endpoint events needed) comparing pooled rivaroxaban doses (2.5 mg twice daily and 5 mg twice daily) and placebo arms within each strata.

5.3.1.10.3 Interim Analyses and Stopping Rules

One interim analysis was to be performed to assess study results for overwhelming efficacy when approximately 70% (688) of the planned total number of best available (adjudicated events or investigator reported events when not adjudicated) or adjudicated primary efficacy endpoint events (a mixture of adjudicated and nonadjudicated events) had occurred. The IDMC reviewed the results of the interim analysis on January 12, 2011 after 762 efficacy events had occurred.

The Independent Data Monitoring Committee (IDMC) Charter stated that the study could be stopped early for overwhelming superiority of rivaroxaban with consistency across strata. A Haybittle-Peto boundary (one-sided p-value < 0.0001; z-value > 3.719) was to be used as a stopping boundary for pooled rivaroxaban doses and individual rivaroxaban doses vs. placebo primary efficacy analyses, and small adjustments were to be required only for the final primary efficacy analyses (the final primary efficacy analyses would be evaluated using a two-sided α=0.0499982).

Overwhelming efficacy could be based on combined strata and stratum 2 primary composite analyses with both doses pooled. Per the Independent Data Monitoring Committee Charter, Amendment #1 (September 27, 2010), the following stopping guidelines would also be considered to confirm the appropriateness of stopping for efficacy

- Both doses were significant or one dose provided compelling evidence of efficacy and there was qualitative interaction for the two doses comparing with placebo, across strata and within stratum 2
- None of the components (CV death, MI, or stroke) showed a trend in the wrong direction, in combined strata and stratum 2
- No major safety concerns including TIMI major/minor bleeds, renal and liver functions, in combined strata and stratum 2
- All cause mortality was either neutral or trending in the right direction (hazard ratio point estimate < 1.0), in combined strata and stratum 2

- Net clinical outcome (composite of the primary efficacy endpoint and non-CABG TIMI major bleed) trended in the right direction
- Sufficient information (both efficacy and safety) to adequately assess differences between the two active doses

The FDA recommended that the trial be stopped early for mortality only.

5.3.1.11 Study Administrative Structure

Study committees included a steering committee with lead investigators from each country/region; an executive committee consisting of members of the academic leadership of the study, one member from Johnson & Johnson Pharmaceutical Research and Development and one member from Bayer HealthCare; an independent data monitoring committee (IDMC); and a Clinical Events Committee (CEC).

5.3.1.11.1 Clinical Events Committee

The CEC was comprised of board-eligible or board-certified cardiologists but did not include any neurologists. The CEC was to confirm and classify the following endpoints in ATLAS ACS 2 TIMI 51:

- Death
- Myocardial infarction
- Stroke
- Severe recurrent ischemia
- Bleeding events

Additionally, the CEC would also confirm and classify the event of stent thrombosis.

The CEC Coordinator identified two CEC members who would review a set of events independently. These two members would subsequently confer and review each event to agree upon a final event classification. If there was no agreement, a third CEC member identified by the CEC Coordinator would review the event and serve as the "tie-breaker."

In addition to the investigator-reported cases of endpoint events, the CEC used triggers to identify efficacy and safety events that may not have been reported but should have been adjudicated. For quality control, the CEC randomly selected 5% (+/- 1%) of the expected total number of primary efficacy and safety events for readjudication.

5.3.1.11.2 Study Termination

The global treatment end date was the date of the accrual of the target 983 primary efficacy endpoint events to be adjudicated as mITT events. Subjects were to continue taking study drug until they had their End of Treatment (EOT) visit. The mITT analysis set censored events that occurred on or after 12:01 a.m. local time on June 3, 2011, the

global treatment end date. Approximately 30 days following the EOT visit, subjects were to follow-up for an End of Study (EOS) visit.

6 Review of Efficacy

Efficacy Summary

1) In All Strata, including subjects treated with aspirin (Stratum 1) and subjects treated with aspirin plus a thienopyridine (Stratum 2), on-treatment plus 30 days (sponsor's modified intent-to-treat (mITT)) and intent-to-treat (ITT) analyses including and excluding Sites 091001, 091019, and 091026 demonstrated that rivaroxaban (combined,[2] 2.5 mg BID, and 5 mg BID) significantly reduced the occurrence of the composite primary endpoint of cardiovascular death, myocardial infarction, or stroke, compared with placebo, in ACS subjects stabilized 1-7 days post index event, as summarized in Table 1. Numerous sensitivity analyses confirmed these results.

Table 11. Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (All Strata)

ALL STRATA	Combined		Rivaroxaban 2.5 mg BID		Rivaroxaban 5 mg BID	
Analysis Set	HR 95% CI	P-value	HR 95% CI	P-value	HR 95% CI	P-value
mITT* excluding Sites 091001, 091019, and 091026	0.84 (0.74, 0.96)	0.008	0.84 (0.72, 0.97)	0.02	0.85 (0.73, 0.98)	0.029
mITT* including Sites 091001, 091019, and 091026	0.85 (0.75, 0.96)	0.011	0.84 (0.72, 0.97)	0.02	0.86 (0.74, 1.00)	0.045
ITT excluding Sites 091001, 091019, and 091026	0.83 (0.73, 0.93)	0.002	0.82 (0.71, 0.95)	0.007	0.83 (0.72, 0.96)	0.011
ITT including Sites 091001, 091019, and 091026	0.83 (0.74, 0.94)	0.003	0.82 (0.71, 0.95)	0.007	0.84 (0.73, 0.97)	0.017

***Sponsor's mITT analysis is an on-treatment plus 30 days analysis**
BID: twice daily; HR: hazard ratio; CEC: Clinical Events Committee; CI: confidence interval; ITT: intent-to- treat; mITT: modified intent-to-treat
Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

2) In Stratum 2 (subjects treated with aspirin plus a thienopyridine), rivaroxaban (combined and 2.5 mg BID) significantly reduced the occurrence of the primary endpoint. Rivaroxaban 5 mg BID was not statistically significant in reducing the occurrence of the primary endpoint.

[2]Rivaroxaban combined = rivaroxaban 2.5 mg BID dose group + rivaroxaban 5 mg BID dose group

Table 12. Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (Stratum 2)

STRATUM 2 (Aspirin + Thienopyridine)	Combined		Rivaroxaban 2.5 mg BID		Rivaroxaban 5 mg BID	
Analysis Set	**HR 95% CI**	**P-value**	**HR 95% CI**	**P-value**	**HR 95% CI**	**P-value**
mITT* excluding Sites 091001, 091019, and 091026	0.86 (0.75, 0.98)	0.025	0.85 (0.72, 0.99)	0.039	0.87 (0.74, 1.02)	0.076
mITT* including Sites 091001, 091019, and 091026	0.86 (0.76, 0.99)	0.032	0.85 (0.72, 0.99)	0.038	0.88 (0.75, 1.03)	0.11
ITT excluding Sites 091001, 091019, and 091026	0.83 (0.73, 0.94)	0.004	0.82 (0.71, 0.96)	0.011	0.84 (0.72, 0.97)	0.02
ITT including Sites 091001, 091019, and 091026	0.84 (0.74, 0.95)	0.006	0.82 (0.71, 0.96)	0.011	0.85 (0.73, 0.99)	0.031

***Sponsor's mITT analysis is an on-treatment plus 30 days analysis**
BID: twice daily; CI: confidence interval; HR: hazard ratio; ITT: intent-to- treat; mITT: modified intent-to-treat
Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

3) The findings in All Strata and Stratum 2 were driven primarily by a reduction in CV deaths, particularly on rivaroxaban 2.5 mg BID, and to a lesser extent by a reduction in MI.

4) Compared to 2.5 mg BID, rivaroxaban 5 mg BID increased the risk of all bleeding events without providing additional efficacy. Further, rivaroxaban 5 mg BID improved MI but not CV death which was somewhat unexpected.

5) With respect to reducing all-cause mortality, rivaroxaban 2.5 mg BID was nominally statistically significant. However, rivaroxaban 5 mg BID was not effective and combined rivaroxaban doses were not robust statistically in reducing all-cause mortality. The interpretation of the mortality findings depended on which analysis sets were used and whether sites 091001, 091019, and 091026 were included.

6) Given the inconsistent results between rivaroxaban 2.5 mg BID and rivaroxaban 5 mg BID with respect to CV death and all-cause mortality, I do not recommend a mortality claim.

7) Given the small sample size, data from ATLAS and TIMI 46 are insufficient to determine whether the use of rivaroxaban 2.5 mg BID in Stratum 1 subjects (aspirin) would be beneficial. These subjects may need rivaroxaban 5 mg BID or a $P2Y_{12}$ inhibitor instead.

6.1 Indication

The sponsor seeks approval for XARELTO 2.5 mg BID and the following indication:

> "XARELTO is a factor Xa inhibitor indicated
>
> - To reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) [ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA) in combination with aspirin alone or with aspirin plus a thienopyridine (clopidogrel or ticlopidine), XARELTO has been shown to reduce the risk of a combined endpoint of cardiovascular (CV) death, myocardial infarction (MI) or stroke. The difference between treatments was driven by CV death and MI."

6.1.1 Methods

This efficacy review focuses on results of the ATLAS ACS 2 TIMI 51 trial.

6.1.2 Demographics

Baseline demographic and disease-related parameters are displayed in Table 13. Overall, baseline characteristics were balanced between treatment groups. Approximately 50% of randomized subjects had index STEMIs. In ATLAS, Eastern Europe enrolled most of the subjects.

Table 13. Demographic and Baseline Characteristics (All Randomized Subjects) (ATLAS)

ALL STRATA	Rivaroxaban			Placebo	Total
	2.5 mg BID	5 mg BID	Combined		
	(N = 5174)	(N = 5176)	(N = 10350)	(N = 5176)	(N = 15526)
Age (years)					
mean ± SD	**61.8 ± 9.2**	**61.9 ± 9.0**	**61.9 ± 9.1**	**61.5 ± 9.4**	**61.8 ± 9.2**
median	**61.0**	**61.0**	**61.0**	**61.0**	**61.0**
25^{th}, 75^{th} percentile	**56, 68**	**56, 68**	**56, 68**	**56, 68**	**56, 68**
≥ 75 years (%)	**9.0**	**8.5**	**8.8**	**9.6**	**9.0**
Female sex (%)	**25.1**	**25.8**	**25.4**	**25.0**	**25.3**
Ethnicity (%)					
Caucasian	**73.4**	**73.7**	**73.6**	**73.3**	**73.5**
Black	**0.7**	**0.7**	**0.7**	**0.8**	**0.7**
Asian	**21.2**	**20.4**	**20.8**	**20.8**	**20.8**
Other	**4.7**	**5.2**	**4.9**	**5.0**	**4.9**

ALL STRATA	Rivaroxaban			Placebo	Total
	2.5 mg BID	5 mg BID	Combined		
	(N = 5174)	(N = 5176)	(N = 10350)	(N = 5176)	(N = 15526)
Geographical Region					
Eastern Europe	39.5	39.1	39.3	38.8	39.1
Western Europe	13.7	15.0	14.3	14.7	14.4
North America	5.2	5.7	5.4	6.0	5.6
South America	10.6	11.3	10.9	10.4	10.8
Asia	21.0	20.2	20.6	20.6	20.6
Others	10.1	8.8	9.5	9.6	9.5
Admitting Diagnosis (%)					
STEMI	50.3	49.9	50.1	50.9	50.3
NSTEMI	25.5	25.8	25.7	25.6	25.6
Unstable Angina	24.2	24.3	24.2	23.6	24.0
Diabetes Mellitus (%)	32.3	31.8	32.0	31.8	32.0
Prior MI (%)	26.3	27.1	26.7	27.3	26.9
Prior Stroke (%)	1.9	1.9	1.9	1.7	1.8
Prior TIA (%)	0.8	1.0	0.9	0.9	0.9

Other pertinent baseline characteristics for All Strata are displayed in Table 14. In contrast to the trial population in which 25% of subjects were treated for index STEMI with fibrinolytic therapy, approximately 6% of subjects only in North America received this therapy. Note that most subjects had elevated cardiac biomarkers at the index event. It appears that a MI decision limit as opposed to a 99th percentile was used to determine whether a subject had an index MI, as unstable angina is often defined as being cardiac biomarker negative. If the 99th percentile cut-off was used for the definition of MI, many subjects with unstable angina at the index event would have had to be reclassified as MIs.

Table 14. Other Pertinent Baseline Characteristics (All Randomized Subjects) (ATLAS)

ALL STRATA	Rivaroxaban			Placebo	Total
	2.5 mg BID	5 mg BID	Combined		
Prior Hypertension					
N	5174	5176	10350	5174	15524
(%)	67.1	67.6	67.3	67.5	67.4
Unstable Angina					
N	1252	1257	2509	1221	3730
TIMI Risk Score (%)					
0-2	3.8	3.9	3.9	3.9	3.9
3-4	79.7	78.4	79.0	78.0	78.7
≥ 5	16.5	17.7	17.1	18.1	17.4

ALL STRATA	Rivaroxaban			Placebo	Total
	2.5 mg BID	5 mg BID	Combined		
Elevation in Cardiac Biomarkers at Index Event					
N	5170	5173	10343	5174	15517
(%)	81.8	81.6	81.7	82.9	82.1
Fibrinolytic Therapy given for Index STEMI					
N	2600	2584	5184	2632	7816
(%)	25.9	24.5	25.2	26.4	25.6
Revascularization Procedure for Index Event					
N	5174	5175	10349	5176	15525
(%)	60.6	60.3	60.5	60.4	60.5
Baseline PCI for Index Event					
N	5174	5175	10349	5176	15525
(%)	60.2	60.0	60.1	59.9	60.1
Baseline CABG for Index Event					
N	5174	5175	10349	5176	15525
(%)	0.4	0.3	0.4	0.5	0.4
Baseline Creatinine Clearance (mL/min) (%)					
N	5111	5104	10215	5120	15335
< 30	0.5	0.4	0.5	0.6	0.5
≥ 30 - < 50	6.7	6.2	6.5	6.8	6.6
≥ 50 - ≤ 80	34.8	36.2	35.5	34.1	35.0
> 80	58.0	57.2	57.6	58.4	57.9

6.1.2.1 Key Differences between Stratum 1 and Stratum 2 (Demographic and Baseline Characteristics)

Key differences between Stratum 1 and Stratum 2 are displayed in Table 15. Compared to Stratum 2, subjects in Stratum 1 tended to have a higher burden of comorbid disease. Compared to Stratum 2, a higher percentage of subjects in Stratum 1 were age ≥ 75 years, had unstable angina for the index event and TIMI Risk Scores ≥ 5, underwent CABG for index revascularization, and had a prior history of diabetes mellitus, hypertension, myocardial infarction, stroke, and TIA.

Stratum 2 subjects were more likely to have elevated cardiac biomarkers and undergo PCI for the index event.

Table 15. Key Differences (%) between Stratum 1 and Stratum 2 (ATLAS)

STRATUM	Rivaroxaban			Placebo	Total
	2.5 mg BID	5 mg BID	Combined		
Age ≥ 75					
Stratum 1, N	349	349	698	355	1053
(%)	15.8	10.6	13.2	21.1	15.9
Stratum 2, N	4825	4827	9652	4821	14473
(%)	8.5	8.4	8.4	8.8	8.6
Admitting Diagnosis					
Stratum 1, N	349	349	698	355	1053
STEMI (%)	22.1	13.5	17.8	16.3	17.3
NSTEMI (%)	22.1	22.3	22.2	26.8	23.7
UA (%)	55.9	64.2	60.0	56.9	59.0
Stratum 2, N	4825	4827	9652	4821	14473
STEMI (%)	52.3	52.6	52.4	53.4	52.8
NSTEMI (%)	25.8	26.0	25.9	25.5	25.8
UA (%)	21.9	21.4	21.7	21.1	21.5
Unstable Angina					
Stratum 1, N	195	224	419	202	621
TIMI Risk Score					
0-2	2.6	2.2	2.4	4.0	2.9
3-4	77.4	80.4	79.0	72.8	77.0
≥ 5	20.0	17.4	18.6	23.3	20.1
Stratum 2, N	1057	1033	2090	1019	3109
TIMI Risk Score					
0-2	4.1	4.3	4.2	3.9	4.1
3-4	80.1	77.9	79.0	79.0	79.0
≥ 5	15.8	17.8	16.8	17.1	16.9
Elevation in Cardiac Biomarkers at Index Event					
Stratum 1, N	349	349	698	355	1053
(%)	52.1	44.4	48.3	55.8	50.8
Stratum 2, N	4821	4824	9645	4819	14464
(%)	83.9	84.3	84.1	84.9	84.4
Fibrinolytic Therapy given for Index STEMI					
Stratum 1, N	77	47	124	58	182
(%)	31.2	29.8	30.6	24.1	28.6
Stratum 2, N	2523	2537	5060	2574	7634
(%)	25.8	24.4	25.1	26.5	25.6

STRATUM	Rivaroxaban			Placebo	Total
	2.5 mg BID	5 mg BID	Combined		
Revascularization Procedure for Index Event					
Stratum 1, N	349	349	698	355	1053
(%)	6.9	3.7	5.3	9.3	6.6
Stratum 2, N	4825	4826	9651	4821	14472
(%)	64.5	64.4	64.5	64.2	64.4
Baseline PCI for Index Event					
Stratum 1, N	349	349	698	355	1053
(%)	5.7	2.3	4.0	6.5	4.8
Stratum 2, N	4825	4826	9651	4821	14472
(%)	64.2	64.2	64.2	63.8	64.1
Baseline CABG for Index Event					
Stratum 1, N	349	349	698	355	1053
(%)	1.1	1.4	1.3	2.8	1.8
Stratum 2, N	4825	4826	9651	4821	14472
(%)	0.4	0.2	0.3	0.3	0.3
Baseline Diabetes					
Stratum 1, N	349	349	698	355	1053
(%)	39.8	39.3	39.5	40.0	39.7
Stratum 2, N	4825	4827	9652	4821	14473
(%)	31.7	31.3	31.5	31.2	31.4
Prior MI					
Stratum 1, N	349	349	698	355	1053
(%)	38.4	41.0	39.7	33.2	37.5
Stratum 2, N	4825	4827	9652	4821	14473
(%)	25.5	26.1	25.8	26.9	26.2
Prior Stroke					
Stratum 1, N	349	349	698	355	1053
(%)	16.3	15.2	15.8	13.8	15.1
Stratum 2, N	4825	4827	9652	4821	14473
(%)	0.9	0.9	0.9	0.8	0.9
Prior TIA					
Stratum 1, N	349	349	698	355	1053
(%)	3.7	4.0	3.9	5.6	4.5
Stratum 2, N	4825	4827	9652	4821	14473
(%)	0.6	0.8	0.7	0.6	0.6

STRATUM	Rivaroxaban			Placebo	Total
	2.5 mg BID	5 mg BID	Combined		
Prior Hypertension					
Stratum 1, N	**349**	**349**	**698**	**355**	**1053**
(%)	**83.1**	**85.4**	**84.2**	**87.3**	**85.3**
Stratum 2, N	**4825**	**4827**	**9652**	**4819**	**14471**
(%)	**65.9**	**66.3**	**66.1**	**66.1**	**66.1**
Baseline Creatinine Clearance (mL/min) (%)					
Stratum 1, N	**343**	**341**	**684**	**352**	**1036**
< 30	**1.5**	**0.6**	**1.0**	**2.3**	**1.4**
≥ 30 - < 50	**12.8**	**8.8**	**10.8**	**16.2**	**12.6**
≥ 50 - ≤ 80	**34.7**	**42.8**	**38.7**	**35.2**	**37.5**
> 80	**51.0**	**47.8**	**49.4**	**46.3**	**48.4**
Stratum 2, N	**4768**	**4763**	**9531**	**4768**	**14229**
< 30	**0.4**	**0.4**	**0.4**	**0.5**	**0.4**
≥ 30 - < 50	**6.3**	**6.0**	**6.1**	**6.1**	**6.1**
≥ 50 - ≤ 80	**34.8**	**35.7**	**35.3**	**34.1**	**34.9**
> 80	**58.5**	**57.9**	**58.2**	**59.3**	**58.6**

Stratum 1 (aspirin).
Stratum 2 (aspirin + thienopyridine).
CABG: coronary artery bypass graft surgery; NSTEMI: non-ST-elevation myocardial infarction; PCI; percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; UA: unstable angina;

6.1.2.2 Geographical Differences between Stratum 1 and Stratum 2

A higher percentage of eastern Europeans were enrolled in Stratum 1 than Stratum 2. Additionally, a higher percentage of subjects in Western Europe, North America, and Asia were enrolled in Stratum 2.

Table 16. Geographical Differences between Strata

Geographical Region	Stratum 1	Stratum 2
Eastern Europe	59.4	37.6
Western Europe	4.6	15.2
North America	1.8	5.9
South America	12.8	10.6
Asia	12.3	21.2
Others	9.2	9.5
Source: adsl.xpt		

6.1.2.3 Time from Index Event to Randomization

In All Strata, the median time from index event to randomization was 4.7 days for all treatment groups, as shown in Table 17.

Table 17. Time from Index Event to Randomization (Days) (ATLAS)

Time from Index Event to Randomization (days)	Rivaroxaban			Placebo	Total
	2.5 mg BID	5 mg BID	Combined		
All Strata	(N = 5174)	(N = 5176)	(N =10350)	(N = 5176)	(N = 15526)
Mean ± SD	4.7 ± 1.8	4.6 ± 1.8	4.7 ± 1.8	4.7 ± 1.8	4.7 ± 1.8
Median	4.7	4.7	4.7	4.7	4.7
Minimum, Maximum	(0, 15)	(0, 13)	(0, 15)	(0, 19)	(0, 19)
Stratum 1	(N = 349)	(N = 349)	(N = 698)	(N = 355)	(N = 1053)
Mean ± SD	4.9 ± 1.7	4.7 ± 1.7	4.8 ± 1.7	4.8 ± 1.8	4.8 ± 1.7
Median	5.0	4.9	5.0	4.9	4.9
Minimum, Maximum	(1, 10)	(1, 13)	(1, 13)	(1, 11)	(1, 13)
Stratum 2	(N = 4825)	(N = 4827)	(N = 9652)	(N = 4821)	(N = 14,473)
Mean ± SD	4.7 ± 1.8	4.6 ± 1.8	4.7 ± 1.8	4.7 ± 1.8	4.7 ± 1.8
Median	4.7	4.7	4.7	4.7	4.7
Minimum, Maximum	(0, 15)	(0, 13)	(0, 15)	(0, 19)	(0, 19)

6.1.2.4 Time from Randomization to First Dose of Study Drug

For All Strata, the median time from randomization to first dose of study drug was approximately 7 hours, as shown in Table 18.

Table 18. Time from Randomization to First Dose of Study Drug (Days) (ATLAS)

Time from Randomization to First Dose of Study Drug (days)	Rivaroxaban			Placebo	Total
	2.5 mg BID	5 mg BID	Combined		
All Strata	(N = 5115)	(N = 5110)	(N = 10225)	(N = 5125)	(N = 15350)
Mean ± SD	0.30 ± 0.57	0.29 ± 0.38	0.29 ± 0.48	0.30 ± 0.40	0.29 ± 0.46
Median	0.28	0.28	0.28	0.28	0.28
Minimum, Maximum	(0, 27.1)	(0, 14.28)	(0, 27.1)	(0, 8)	(0, 27.1)
Stratum 1	(N = 343)	(N = 342)	(N = 685)	(N = 352)	(N = 1037)
Mean ± SD	0.27 ± 0.29	0.27 ± 0.30	0.27 ± 0.30	0.28 ± 0.34	0.27 ± 0.31
Median	0.25	0.28	0.27	0.28	0.27
Minimum, Maximum	(0, 3.2)	(0, 4.5)	(0, 4.5)	(0, 5.0)	(0, 5.0)

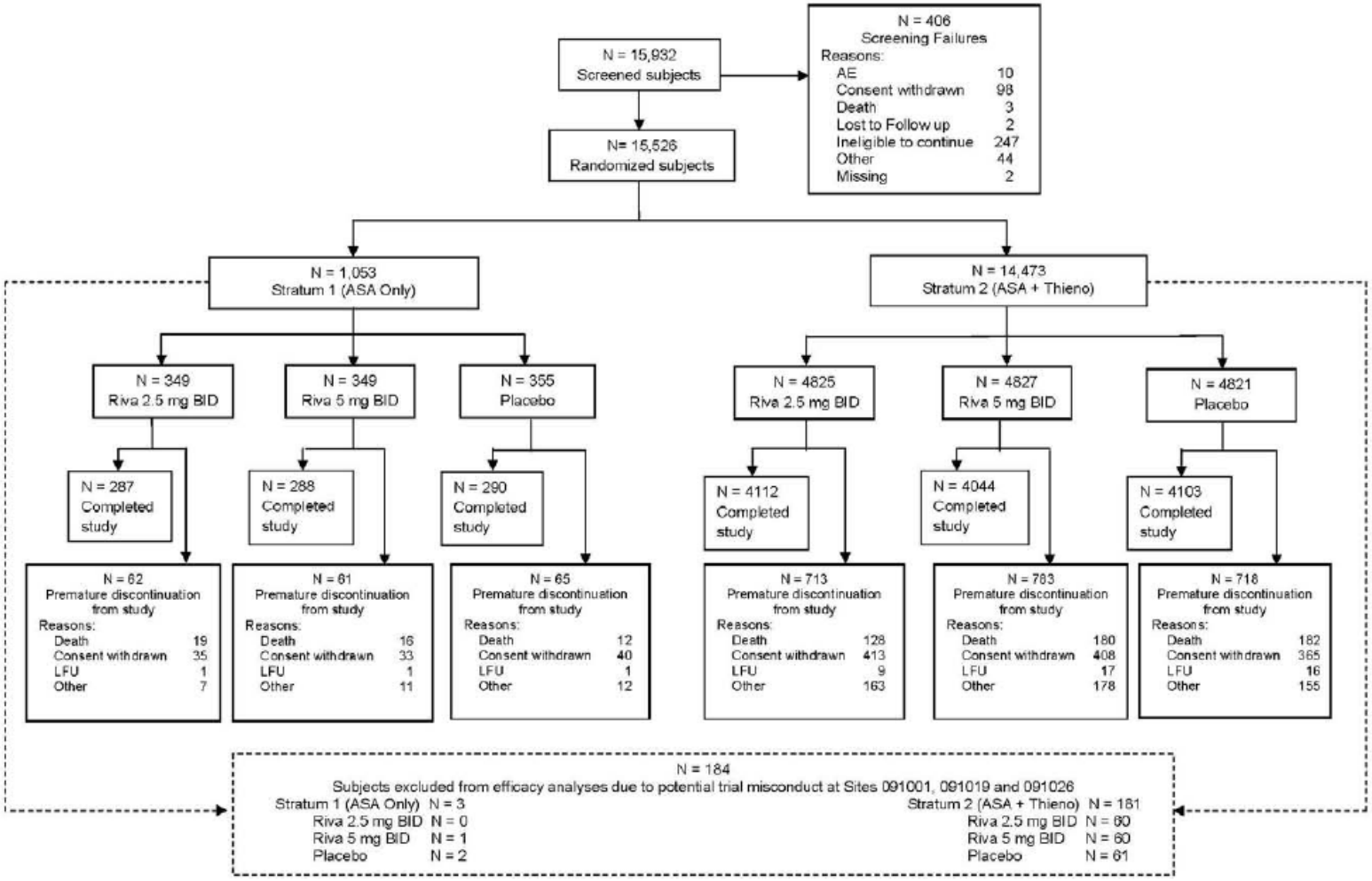
Time from Randomization to First Dose of Study Drug (days)	Rivaroxaban			Placebo	Total
	2.5 mg BID	5 mg BID	Combined		
Stratum 2	**(N = 4772)**	**(N = 4768)**	**(N = 9540)**	**(N = 4773)**	**(N = 14313)**
Mean ± SD	**0.30 ± 0.58**	**0.29 ± 0.39**	**0.29 ± 0.49**	**0.30 ± 0.40**	**0.30 ± 0.47**
Median	**0.28**	**0.28**	**0.28**	**0.28**	**0.28**
Minimum, Maximum	**(0, 27.1)**	**(0, 14.3)**	**(0, 27.1)**	**(0, 8.0)**	**(0, 27.1)**
Source: adsl.xpt					

6.1.3 Subject Disposition

Subject disposition is displayed in Figure 3. Originally, it was estimated that approximately 13,570 subjects (2,079 subjects in Stratum 1 and 11,491 subjects in Stratum 2) were needed to reach the 983 primary efficacy endpoint events. Ultimately, a total of 15,932 subjects were screened and 15,526 subjects (1,053 in Stratum 1 and 14,473 in Stratum 2) were randomized in the study. Subjects were treated for a median duration of 397, 377, and 399 days in the rivaroxaban 2.5 mg BID, rivaroxaban 5 mg BID, and placebo treatment groups, respectively.

Of the 15,526 subjects randomized, 13,124 (84.5%) subjects completed the study. In Stratum 1, 287 (82.2%), 288 (82.5%), and 290 (81.7%) subjects completed the trial on rivaroxaban 2.5 mg BID, rivaroxaban 5 mg BID, and placebo, respectively. In Stratum 2, 4112 (85.2%), 4044 (83.8%), and 4103 (85.1%) subjects completed the trial on rivaroxaban 2.5 mg BID, rivaroxaban 5 mg BID, and placebo, respectively.

Figure 3. Subject Disposition (ATLAS)



(Sponsor, Clinical Study Report, Figure 3, page 84)

A total of 2402 (15.5%) subjects prematurely discontinued from the trial, including 537 subjects (3.5%) who died, 1294 (8.3%) subjects who withdrew consent, 45 (0.3%) subjects who were lost to follow-up and 526 (3.4%) subjects who discontinued for other reasons, as shown in Table 19. The main reason for premature discontinuation from the trial was "consent withdrawn."

Of the 1294 subjects who withdrew consent, 108 (8%) were in Stratum 1 and 1186 (92%) were in Stratum 2. In Stratum 1, most of the "consent withdrawns" were in the placebo group, and in Stratum 2, most were in the rivaroxaban treatment groups.

For all randomized subjects (N=15526), the "consent withdrawn" rates for the two strata by dose are as follows: Stratum 1: rivaroxaban 2.5 mg BID: 35/349 (10%), rivaroxaban 5 mg BID: 33/349 (10%), and placebo: 40/355 (11%); Stratum 2: rivaroxaban 2.5 mg BID: 413/4825 (9%), rivaroxaban 5 mg BID: 408/4827 (9%), and placebo: 365/4821 (8%). In total, consent was withdrawn in 9% of rivaroxaban combined subjects and in 8% of placebo subjects.

Table 19. Primary Reasons for Discontinuation (All Randomized Subjects) (ATLAS)

ALL STRATA	**Rivaroxaban**				
Status **Standard Disposition Term** **Reason**	**2.5 mg BID (N=5174) n(%)**	**5 mg BID (N=5176) n(%)**	**Combined (N=10350) n(%)**	**Placebo (N=5176) n(%)**	**Total (N=15526) n (%)**
Completed study	**4399 (85.0)**	**4332 (83.7)**	**8731 (84.4)**	**4393 (84.9)**	**13124 (84.5)**
Completed double-blind treatment period	3711 (71.7)	3570 (69.0)	7281 (70.3)	3745 (72.4)	11026 (71.0)
Not completed treatment period	688 (13.3)	762 (14.7)	1450 (14.0)	648 (12.5)	2098 (13.5)
Prematurely discontinued from study	**775 (15%)**	**844 (16.3)**	**1619 (15.6)**	**783 (15.1)**	**2402 (15.5)**
Death	147 (2.8)	196 (3.8)	343 (3.3)	194 (3.7)	537 (3.5)
Consent withdrawn	448 (8.7)	441 (8.5)	889 (8.6)	405 (7.8)	1294 (8.3)
Lost to follow-up	10 (0.2)	18 (0.3)	28 (0.3)	17 (0.3)	45 (0.3)
Other	170 (3.3)	189 (3.7)	359 (3.5)	167 (3.2)	526 (3.4)
Closed/retired sites	37 (0.7)	38 (0.7)	75 (0.7)	42 (0.8)	117 (0.8)
Long travel/relocation/welfare	12 (0.2)	15 (0.3)	27 (0.3)	15 (0.3)	42 (0.3)
Medical reasons/ unblinded/ prohibited meds	25 (0.5)	26 (0.5)	51 (0.5)	16 (0.3)	67 (0.4)
Never received study medication	2 (< 0.1)	3 (0.1)	5 (< 0.1)	4 (0.1)	9 (0.1)
Not meeting inclusion/exclusion	25 (0.5)	21 (0.4)	46 (0.4)	16 (0.3)	62 (0.4)
Subject choice/non compliance	69 (1.3)	86 (1.7)	155 (1.5)	74 (1.4)	229 (1.5)
Discontinued subjects include subjects who were not followed-up until the end of study (global treatment end date + 30 days).					

BID: twice daily
Source: ADSL (trlstat) (Verified by Karen A. Hicks, M.D.)

6.1.3.1 Collection of Vital Status Information on Consent Withdrawn Subjects

The sponsor made an attempt to follow-up on the vital status of the 1294 randomized subjects who withdrew consent. Per the sponsor, they were "denied" permission from various health authorities and investigational review boards to contact 1111 of the 1294 subjects. Of the 183 consent withdrawn subjects the sponsor was allowed to contact, 177 subjects were confirmed to be alive. The sponsor was unable to contact six subjects after the global treatment end date. Therefore, overall, the number of consent withdrawn subjects who were confirmed alive was 54, 57, and 66 on rivaroxaban 2.5 mg BID, rivaroxaban 5 mg BID, and placebo, respectively, as shown in Table 20. There were still a large number of consent withdrawn subjects (1117) with unknown vital status at the end of the trial. Approximately 5% of subjects had CV events prior to discontinuation.

Table 20. Status for Consent Withdrawn Subjects at End of Study (All Randomized Subjects) (ALL STRATA) (ATLAS)

ALL STRATA	Rivaroxaban			Placebo (N = 5176) n (%)	Total (N = 15526)
Reason	2.5 mg BID (N = 5174) n (%)	5 mg BID (N = 5176) n (%)	Combined (N = 10350) n (%)		
Consent withdrawn	448	441	889	405	1294
Vital Status: Alive	54 (12.1)	57 (12.9)	111 (12.5)	66 (16.3)	177 (13.7)
Vital Status: Unknown	394 (87.9)	384 (87.1)	778 (87.5)	339 (83.7)	1117 (86.3)
With CV events before discontinuation	23 (5.1)	16 (3.6)	39 (4.4)	22 (5.4)	61 (4.7)
Without CV events before discontinuation	425 (94.9)	425 (96.4)	850 (95.6)	383 (94.6)	1233 (95.3)

BID: twice daily; CV: cardiovascular
Source: Clinical Study Report, Table 10, page 99

Reviewer Comment: *These missing data in ATLAS, especially with respect to vital status, could affect the overall interpretability of this trial. Most missing data are in the rivaroxaban treatment arms. In general, it typically does not take many events to overturn the statistical significance of a study treatment in a clinical trial.*

6.1.4 Analysis of Primary Endpoint and its Components

The primary endpoint was the analysis of the first occurrence of the composite of CV death, MI, or stroke.

6.1.4.1 Primary Endpoint Results in All Strata and Stratum 2

In All Strata, the sponsor's mITT analysis (on-treatment + 30 days) (excluding sites 091001, 091019, and 091026) demonstrated that the rivaroxaban combined dose group significantly reduced the risk of the primary endpoint by 16% (HR = 0.84 and p-value = 0.008) compared to placebo, as shown in Table 21. Rivaroxaban 2.5 mg bid and rivaroxaban 5 mg bid, compared to placebo, also significantly reduced primary endpoint events (HR = 0.84, p = 0.02; and HR = 0.85, p = 0.029, respectively). The Kaplan-Meier plot for the primary efficacy endpoint in All Strata is displayed in Figure 4.

In Stratum 2, rivaroxaban combined doses significantly reduced the risk of the primary endpoint by 14% (HR = 0.86, p = 0.025). Compared to placebo, the rivaroxaban 2.5 mg BID treatment group had significantly fewer primary efficacy endpoint events (HR = 0.85 and p = 0.039). Although rivaroxaban 5 mg BID also reduced primary endpoint events, this reduction was not statistically significant (HR = 0.87, p = 0.076). The Kaplan-Meier plot for the primary efficacy endpoint in Stratum 2 is displayed in Figure 5.

With respect to the components of the primary endpoint, in All Strata and Stratum 2 (aspirin + thienopyridine), combined and individual doses of rivaroxaban demonstrated numerical reductions in CV death and MI, when compared to placebo, as all hazard ratios were less than 1.0. However, in All Strata and Stratum 2, all rivaroxaban treatment groups were inferior to placebo with respect to stroke.

Investigator-reported primary endpoint results for All Strata were similar to the mITT analysis excluding sites 091001, 091019, and 091026 and are displayed in Table 22.

Results for the mITT analysis including sites 091001, 091019, and 091026, are shown in Table 23. These results were similar to the mITT analysis excluding these sites.

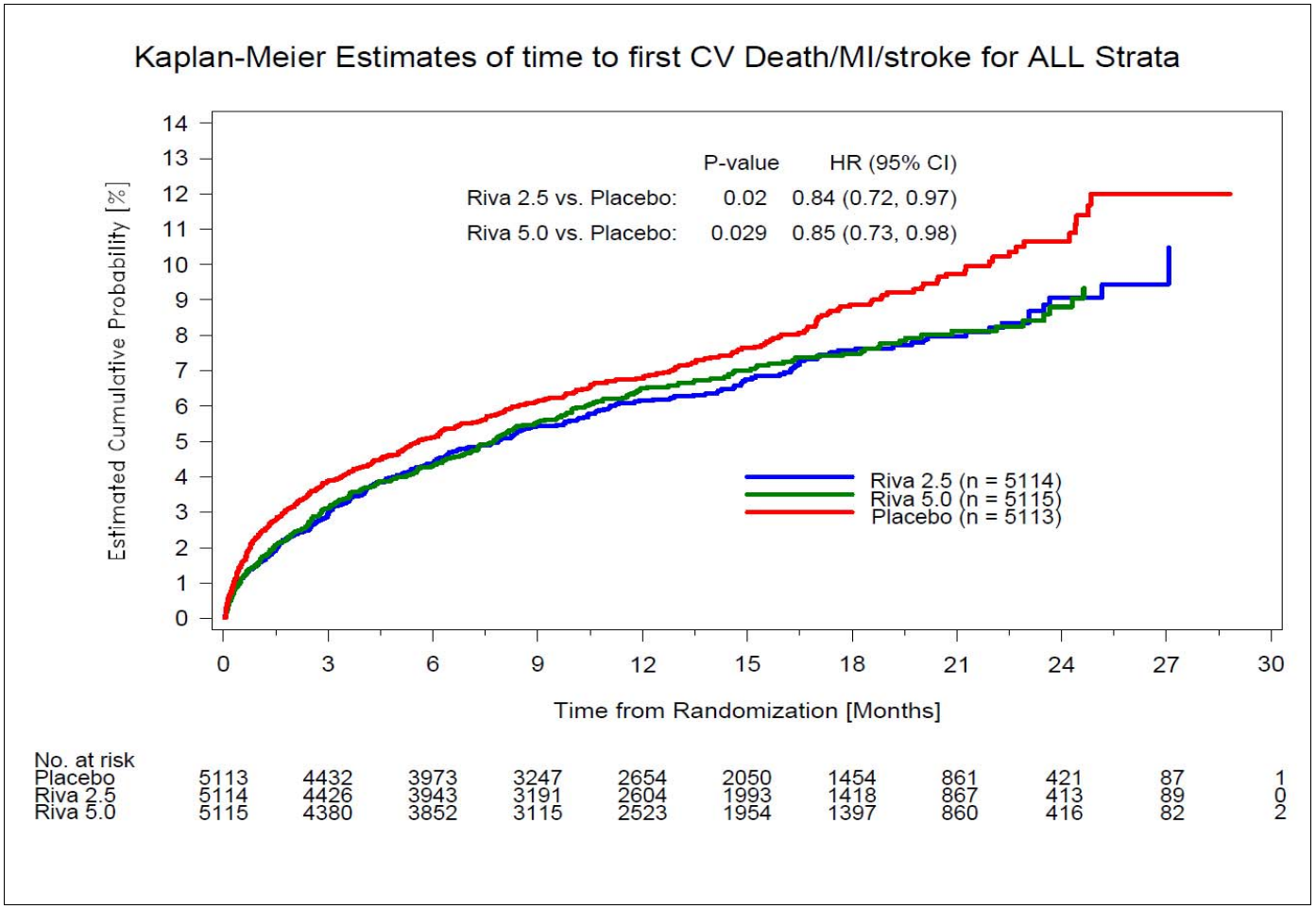
For All Strata, a forest plot for the primary endpoint is displayed in Figure 6. Rivaroxaban (combined, 2.5 mg BID, and 5 mg BID) was consistently superior to placebo, regardless of the analysis set used. Findings were similar in Stratum 2 with the exception of the mITT analyses (including and excluding sites 091001, 091019, and 091026) for rivaroxaban 5 mg BID which were not statistically significant. The forest plot for Stratum 2 is displayed in Figure 7.

Table 21. Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) and its Components as Adjudicated by the CEC (mITT Excluding Sites 091001, 091019, and 091026)

Stratum	Rivaroxaban			Placebo	2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID	5 mg BID	Combined		HR (95% CI)	Log-Rank P-Value	HR (95% CI)	Log-Rank P-Value	HR (95% CI)	Log-Rank P-Value
ALL STRATA	**N = 5114 n (%)**	**N = 5115 n (%)**	**N = 10229 n (%)**	**N = 5113 n (%)**						
Primary Endpoint	313 (6.1)	313(6.1)	626 (6.1)	376 (7.4)	0.84 (0.72, 0.97)	0.02	0.85 (0.73, 0.98)	0.028	0.84 (0.74, 0.96)	0.008
CV death	94 (1.8)	132 (2.6)	226 (2.2)	143 (2.8)	0.66 (0.51, 0.86)	0.002	0.94 (0.75, 1.20)	0.633	0.80 (0.65, 0.99)	0.038
MI	205 (4.0)	179 (3.5)	384 (3.8)	229 (4.5)	0.90 (0.75, 1.09)	0.270	0.79 (0.65, 0.97)	0.020	0.85 (0.72, 1.00)	0.047
Stroke	46 (0.9)	54 (1.1)	100 (1.0)	41 (0.8)	1.13 (0.74, 1.73)	0.562	1.34 (0.90, 2.02)	0.151	1.24 (0.86, 1.78)	0.246
STRATUM 2 (Aspirin + Thienopyridine)	**N = 4765 n (%)**	**N = 4767 n (%)**	**N = 9532 n (%)**	**N = 4760 n (%)**						
Primary Endpoint	286 (6.0)	289 (6.1)	575 (6)	340 (7.1)	0.85 (0.72, 0.99)	0.039	0.87 (0.74, 1.02)	0.076	0.86 (0.75, 0.98)	0.025
CV death	82 (1.7)	123 (2.6)	205 (2.2)	133 (2.8)	0.62 (0.47, 0.82)	0.001	0.95 (0.74, 1.21)	0.669	0.78 (0.63, 0.98)	0.028
MI	189 (4.0)	169 (3.5)	358 (3.8)	207 (4.4)	0.92 (0.76, 1.12)	0.402	0.83 (0.68, 1.02)	0.078	0.88 (0.74, 1.04)	0.131
Stroke	44 (0.9)	46 (1.0)	90 (0.7)	34 (0.7)	1.31 (0.84, 2.05)	0.238	1.39 (0.89, 2.16)	0.144	1.35 (0.91, 2.00)	0.137

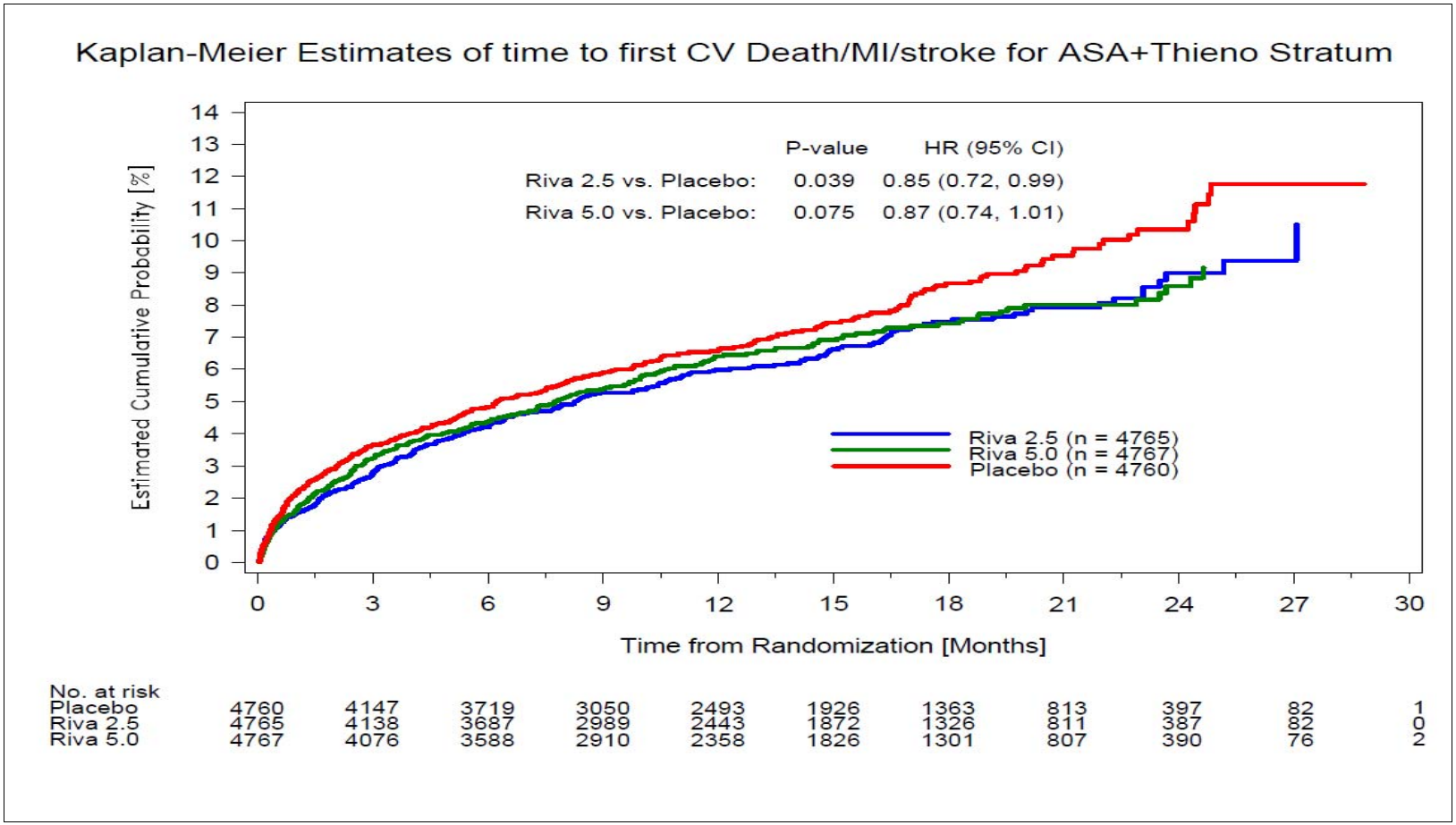
CEC: Clinical Events Committee; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; mITT: modified intent-to-treat. Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

Figure 4. Kaplan-Meier Estimates of the Primary Efficacy Endpoint in All Strata: mITT (Excluding Sites 091001, 091019, and 091026)



Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

Figure 5. Kaplan-Meier Estimates of the Primary Efficacy Endpoint in Stratum 2: mITT (Excluding Sites 091001, 091019, and 091026)



Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

Table 22. Comparison of CEC-Adjudicated and Investigator-Reported Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint and its Components (First Occurrence of Cardiovascular Death, MI, Stroke): mITT Excluding Sites 091001, 091019, and 091026 (ALL STRATA)

ALL STRATA	Rivaroxaban			Placebo	2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID	5 mg BID	Combined		HR (95% CI)	Log-Rank P-Value	HR (95% CI)	Log-Rank P-Value	HR (95% CI)	Log-Rank P-Value
CEC-Adjudicated	**N = 5114 n (%)**	**N = 5115 n (%)**	**N = 10229 n (%)**	**N = 5113 n (%)**						
Primary Endpoint	313 (6.1)	313(6.1)	626 (6.1)	376 (7.4)	0.84 (0.72, 0.97)	0.02	0.85 (0.73, 0.98)	0.028	0.84 (0.74, 0.96)	0.008
CV death	94 (1.8)	132 (2.6)	226 (2.2)	143 (2.8)	0.66 (0.51, 0.86)	0.002	0.94 (0.75, 1.20)	0.633	0.80 (0.65, 0.99)	0.038
MI	205 (4.0)	179 (3.5)	384 (3.8)	229 (4.5)	0.90 (0.75, 1.09)	0.270	0.79 (0.65, 0.97)	0.020	0.85 (0.72, 1.00)	0.047
Stroke	46 (0.9)	54 (1.1)	100 (1.0)	41 (0.8)	1.13 (0.74, 1.73)	0.562	1.34 (0.90, 2.02)	0.151	1.24 (0.86, 1.78)	0.246
Investigator-Reported	**N = 5114 n (%)**	**N = 5115 n (%)**	**N = 10229 n (%)**	**N = 5113 n (%)**						
Primary Endpoint	275 (5.4)	297 (5.8)	572 (5.6)	343 (6.7)	0.81 (0.69, 0.95)	0.007	0.88 (0.76, 1.03)	0.113	0.84 (0.74, 0.97)	0.013
CV death	90 (1.8)	120 (2.3)	210 (2.1)	139 (2.7)	0.65 (0.50, 0.85)	0.002	0.88 (0.69, 1.13)	0.317	0.77 (0.62, 0.95)	0.015
MI	167 (3.3)	157 (3.1)	324 (3.2)	199 (3.9)	0.84 (0.69, 1.04)	0.106	0.80 (0.65, 0.99)	0.039	0.82 (0.69, 0.98)	0.031
Stroke	48 (0.9)	65 (1.3)	113 (1.1)	44 (0.9)	1.10 (0.73, 1.66)	0.641	1.52 (1.03, 2.22)	0.033	1.31 (0.92, 1.85)	0.131

CEC: Clinical Events Committee; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; mITT: modified intent-to-treat. Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

Table 23. Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) and its Components as Adjudicated by the CEC (mITT Including Sites 091001, 091019, and 091026)

Stratum	Rivaroxaban			Placebo	2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID	5 mg BID	Combined		HR (95% CI)	Log-Rank P-Value	HR (95% CI)	Log-Rank P-Value	HR (95% CI)	Log-Rank P-Value
ALL STRATA	**N = 5174 n (%)**	**N = 5176 n (%)**	**N = 10350 n (%)**	**N = 5176 n (%)**						
Primary Endpoint	315 (6.1)	319 (6.2)	634 (6.1)	378 (7.3)	0.84 (0.72, 0.97)	0.020	0.86 (0.74, 1.00)	0.045	0.85 (0.75, 0.96)	0.011
CV death	95 (1.8)	136 (2.6)	231 (2.2)	145 (2.8)	0.66 (0.51, 0.85)	0.001	0.96 (0.76, 1.21)	0.728	0.81 (0.66, 0.99)	0.044
MI	206 (4.0)	181 (3.5)	387 (3.7)	229 (4.4)	0.90 (0.75, 1.09)	0.288	0.80 (0.66, 0.98)	0.027	0.85 (0.72, 1.01)	0.057
Stroke	46 (0.9)	54 (1.0)	100 (1.0)	41 (0.8)	1.13 (0.74, 1.72)	0.565	1.35 (0.90, 2.02)	0.150	1.24 (0.86, 1.78)	0.246
STRATUM 2 (Aspirin + Thienopyridine)	**N = 4825 n (%)**	**N = 4827 n (%)**	**N = 9652 n (%)**	**N = 4821 n (%)**						
Primary Endpoint	288 (6.0)	295 (6.1)	583 (6.0)	342 (7.1)	0.85 (0.72, 0.99)	0.038	0.88 (0.75, 1.03)	0.11	0.86 (0.76, 0.99)	0.032
CV death	83 (1.7)	127 (2.6)	210 (2.2)	135 (2.8)	0.62 (0.47, 0.81)	<0.001	0.96 (0.72, 1.23)	0.768	0.79 (0.64, 0.98)	0.032
MI	190 (3.9)	171 (3.5)	361 (3.7)	207 (4.3)	0.92 (0.76, 1.12)	0.422	0.84 (0.69, 1.03)	0.098	0.88 (0.74, 1.05)	0.154
Stroke	44 (0.9)	46 (1.0)	90 (0.9)	34 (0.7)	1.31 (0.83, 2.04)	0.241	1.39 (0.89, 2.17)	0.144	1.35 (0.91, 2.00)	0.136

CEC: Clinical Events Committee; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; mITT: modified intent-to-treat. Verified by Steve Bai, Ph.D., Division of Biometrics I, FDA

Figure 6. Forest Plots of Primary Efficacy Results by Different Analysis Sets (All Strata)

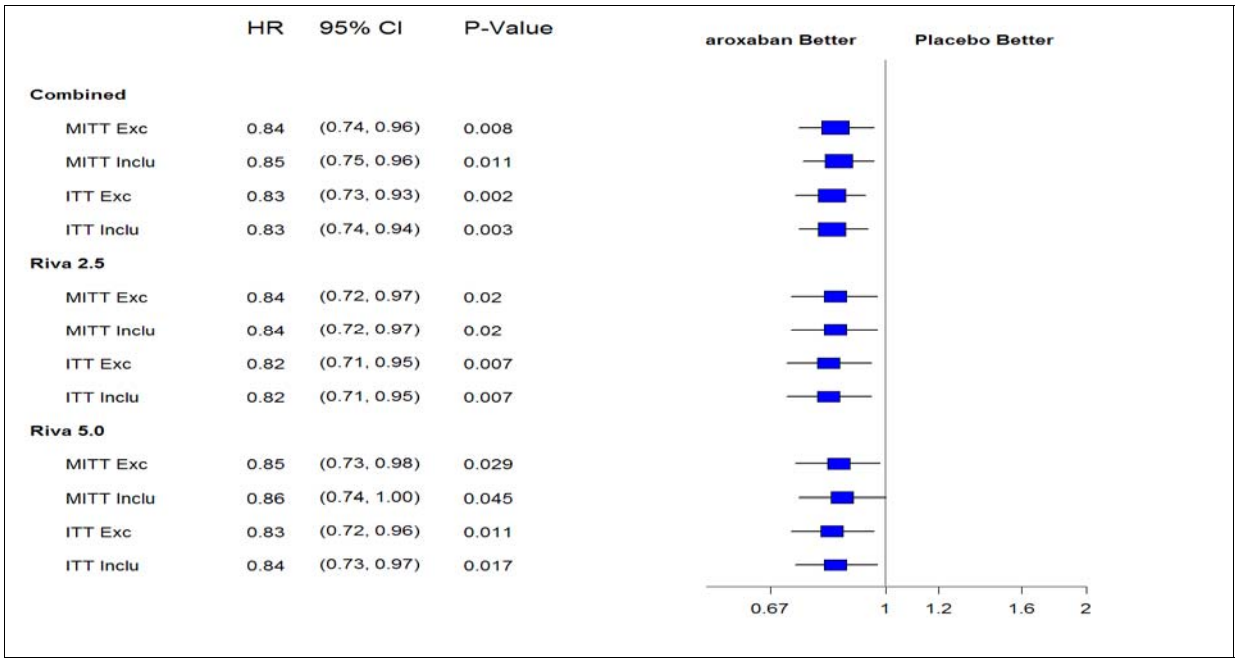
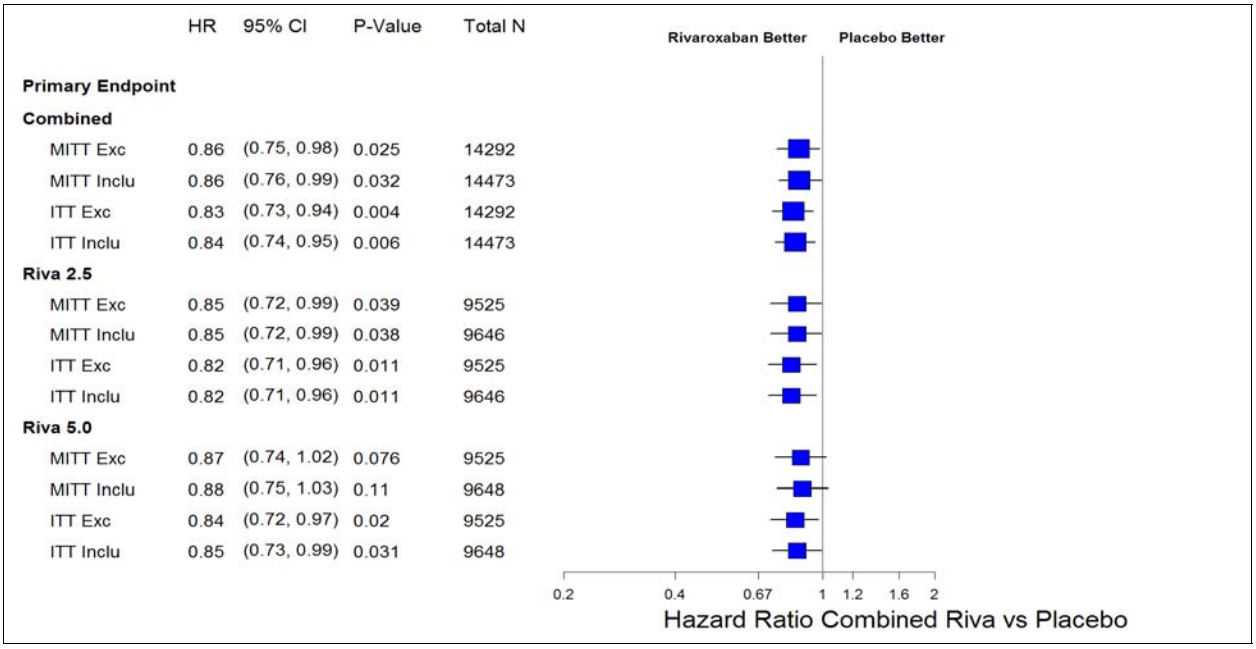


Figure 7. Forest Plots of Primary Efficacy Results by Different Analysis Sets (Stratum 2)



Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

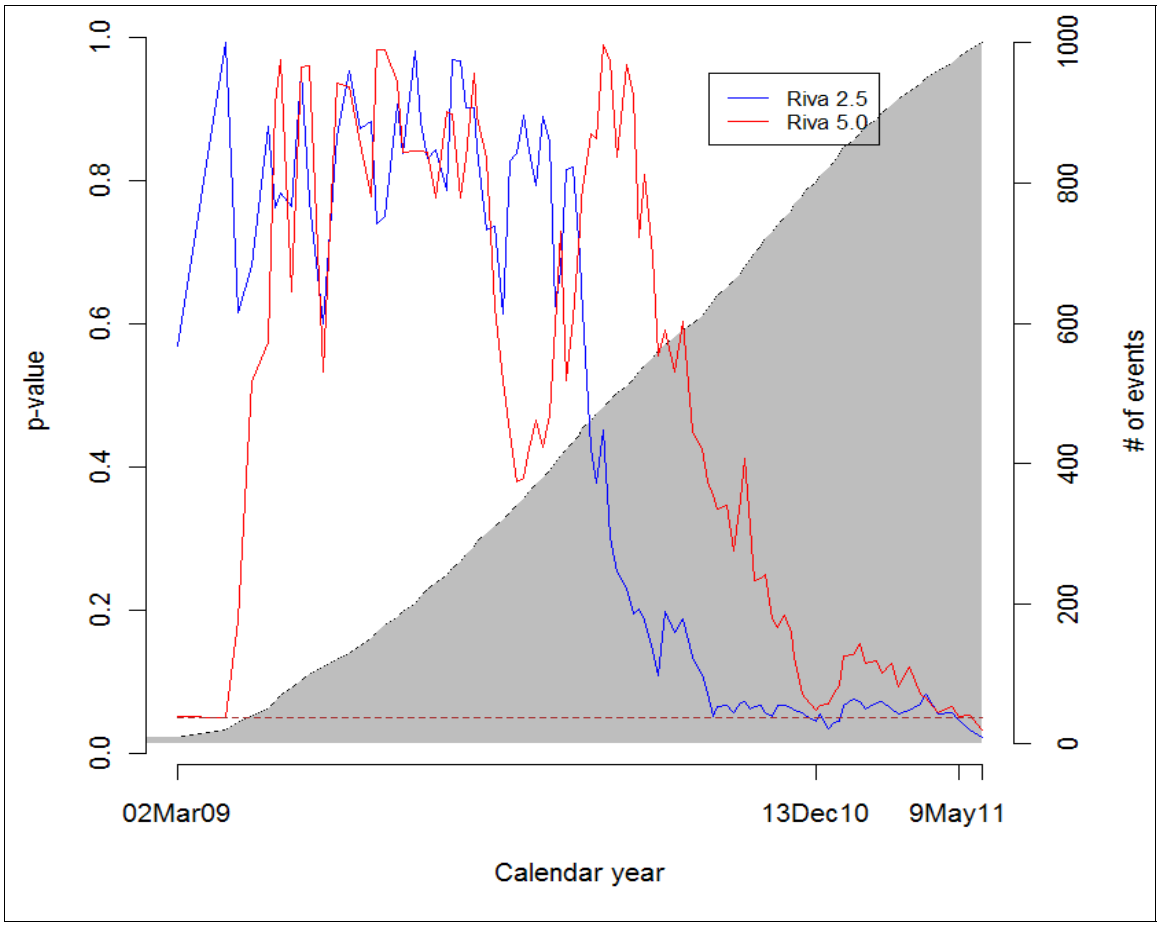
6.1.4.2 Analysis on the Impact of Different End of Trial Dates

In All Strata, statistical significance was achieved for both rivaroxaban doses (2.5 mg BID and 5 mg BID) in the second-half of the trial only.

In All Strata, both rivaroxaban doses (2.5 mg BID and 5 mg BID) were statistically significant in reducing the occurrence of the composite primary endpoint regardless of the analysis set used and inclusion/exclusion of sites 091001, 091019, and 091026.

Dr. Bai conducted an analysis to determine how early statistical significance was established in the trial. In Figure 8, p-values are shown as a function of calendar time of the study for the primary endpoint. The event (censor) status and time to event information were modified such that the current calendar time was assumed to be the end of trial date starting from March 2, 2009 to June 3, 2011, the actual end of trial date. The original Cox regression analysis with treatment as a covariate was conducted for each day. The red curve represents the p-value of rivaroxaban 5 mg BID, and the blue curve represents the p-value of rivaroxaban 2.5 mg BID. Per Figure 8, December 13, 2010 was the first time rivaroxaban 2.5 mg BID crossed the red-dashed horizontal line representing statistical significance at the 0.05 level. May 9, 2011 was the last time the p-value of rivaroxaban 2.5 mg BID stayed above 0.05. Rivaroxaban 5 mg BID achieved statistical significance a few days before the end of the trial only.

Figure 8. Cox Model P-Values of the Primary Composite Endpoint Across Trial Calendar Date (All Strata mITT, Excluding 3 sites)

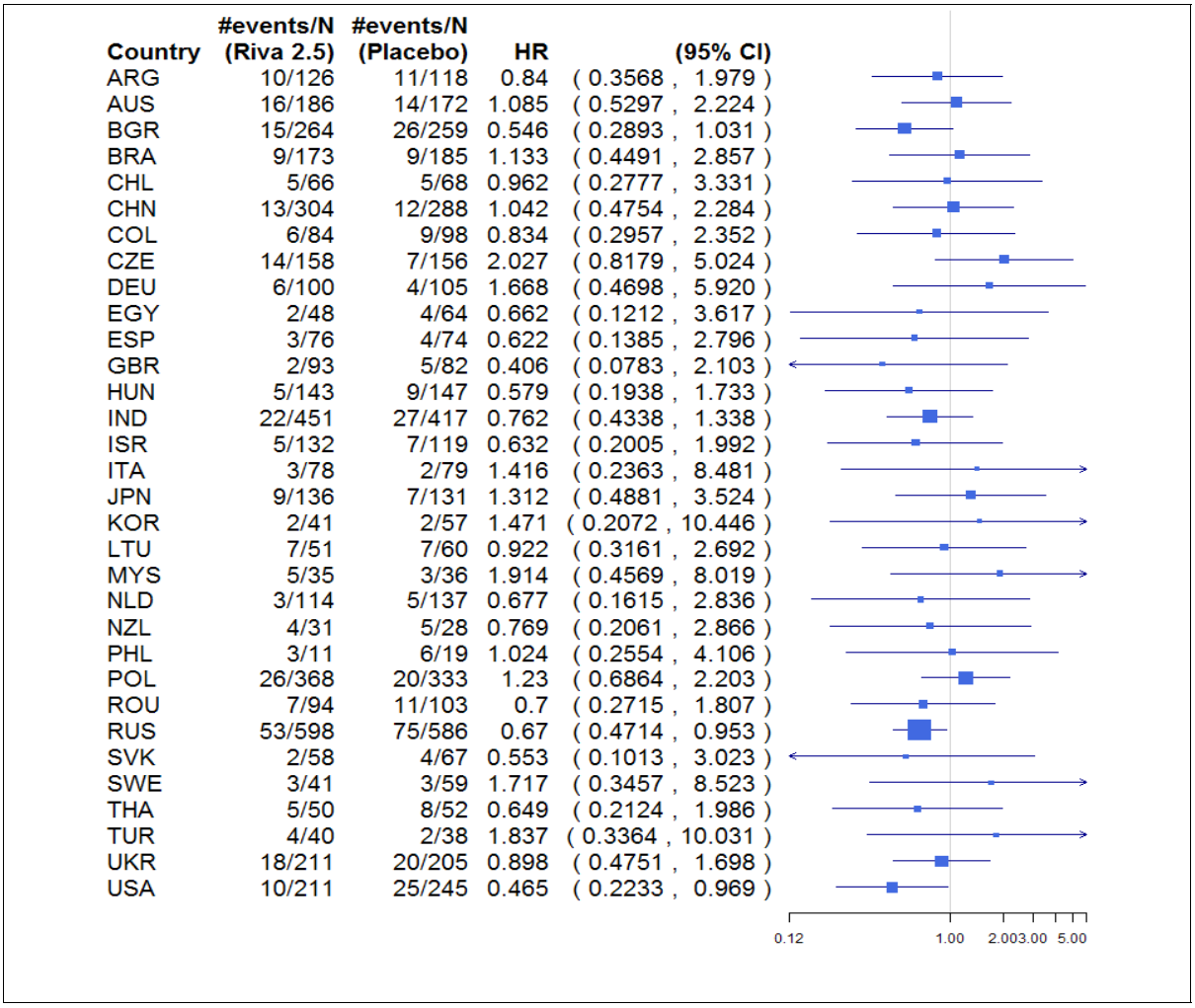


Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

6.1.4.3 Analysis of the Primary Endpoint by Country

ATLAS was conducted in 44 countries at 766 study sites. In All Strata, rivaroxaban 2.5 mg BID was numerically superior to placebo for the primary endpoint in many countries, as shown in Figure 9. Russian sites enrolled the largest number of subjects and contributed most of the primary endpoint events. In both the United States and Russia, rivaroxaban 2.5 mg BID was statistically superior to placebo with respect to the primary endpoint (United States HR 0.465; 95% CI 0.223, 0.969 / Russia HR 0.67; 95% CI 0.471, 0.953).

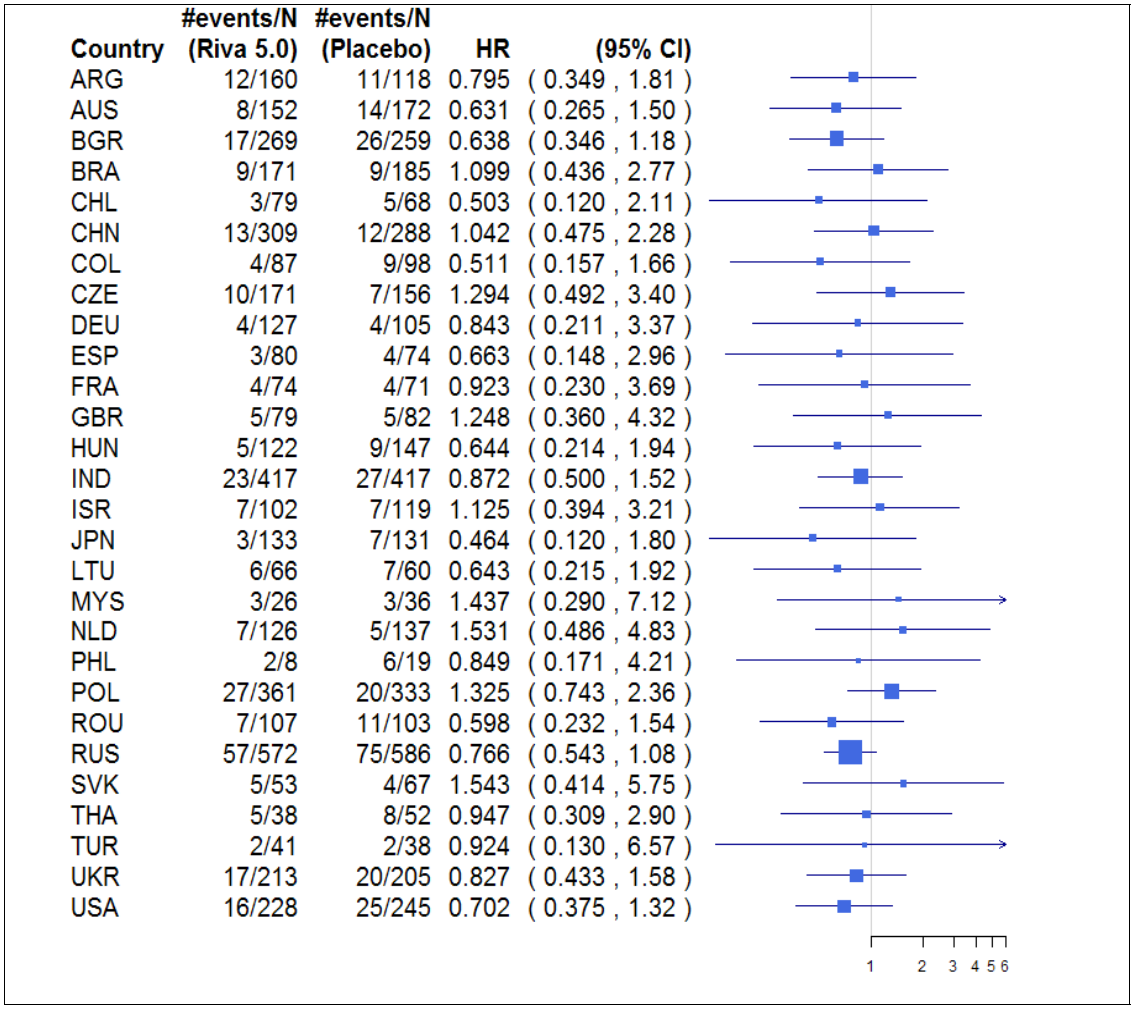
Figure 9. Forest Plots of Hazard Ratio and 95% Confidence Intervals for Primary Endpoint Comparing Rivaroxaban 2.5 mg BID to Placebo by Country (All Strata): mITT (Excluding Sites 091001, 091019, and 091026) (All Strata)



Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

Figure 10 displays the subgroup analyses for rivaroxaban 5 mg BID compared to placebo for the primary endpoint. Russia and the United States demonstrated numerically but not statistically significant results.

Figure 10. Forest Plots of Hazard Ratio and 95% Confidence Intervals for Primary Endpoint Comparing Rivaroxaban 5 mg BID to Placebo by Country (All Strata): mITT (Excluding Sites 091001, 091019, and 091026) (All Strata)



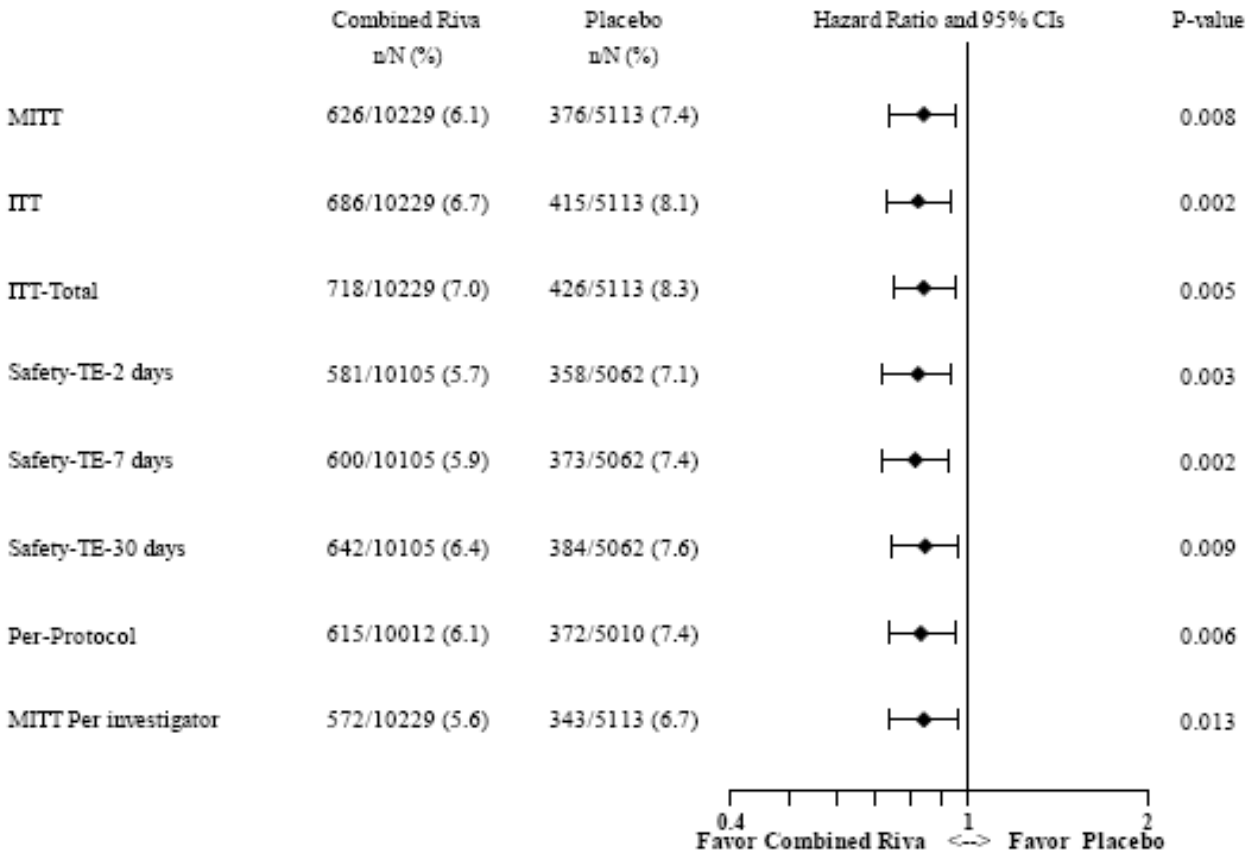
Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

6.1.4.4 Sensitivity Analyses of the Primary Endpoint

In All Strata, excluding sites 091001, 091019, and 091026, numerous sensitivity analyses were consistent with the results of the primary efficacy analysis and confirmed that rivaroxaban (combined, 2.5 mg BID) significantly reduced the risk of the primary endpoint. Sensitivity analyses for rivaroxaban 5 mg BID, excluding sites 091001, 091019, and 091026, demonstrated similar results to the data presented in the Forest

Plot (Figure 6). These sensitivity analyses are displayed in Figure 11, Figure 12, and Figure 13.

Figure 11. Effect of Combined Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (All Strata Excluding Sites 091001, 091019, 091026)



ITT: intent-to-treat ; mITT: modified intent-to-treat; TE: treatment emergent
Source: Sponsor's Clinical Study Report, page 146. Verified by Steve Bai, Ph.D., Division of Biometrics I, FDA.

Figure 12. Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on the Primary Efficacy Endpoint (All Strata Excluding Sites 091001, 091019, 091026)

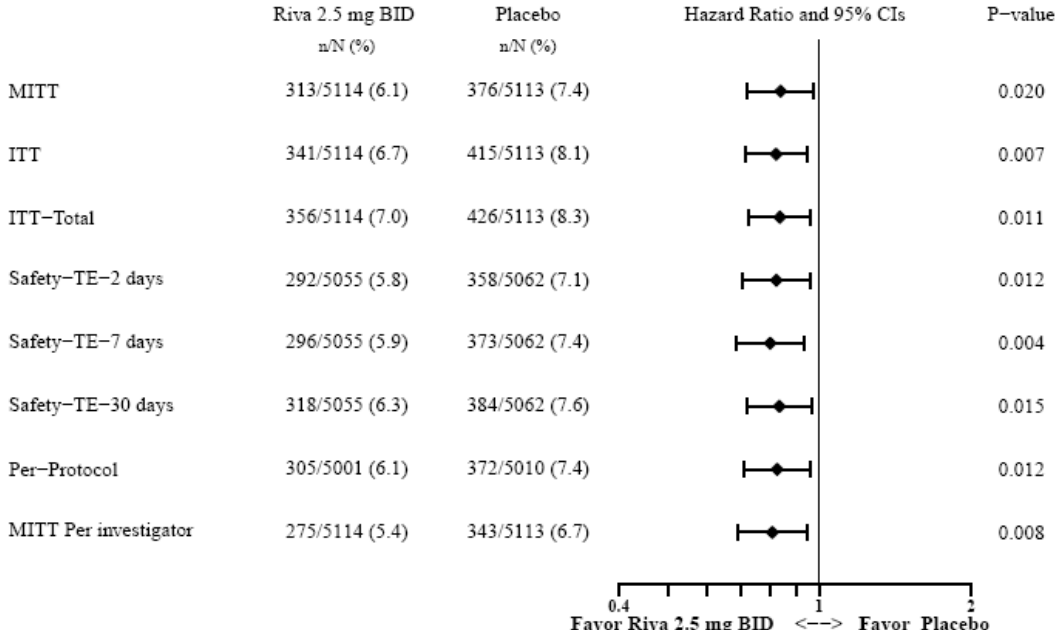
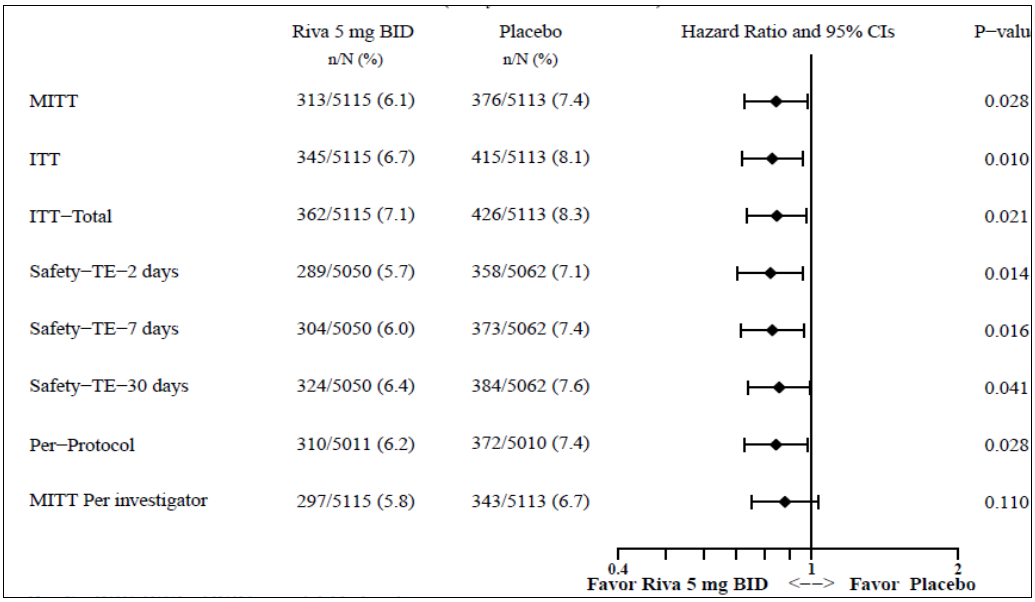


Figure 13. Effect of Rivaroxaban 5.0 mg BID Compared with Placebo on the Primary Efficacy Endpoint (All Strata Excluding Sites 091001, 091019, 091026)



ITT: intent-to-treat ; mITT: modified intent-to-treat; TE: treatment emergent
Source: Sponsor's Clinical Study Report, pages 1483-1484.

6.1.4.5 Stratum 1 (ATLAS and TIMI 46)

6.1.4.5.1 Stratum 1 (TIMI 46)

TIMI 46 was a randomized, multicenter, double-blind, placebo-controlled, dose-escalation and dose-confirmation study designed to evaluate the safety and efficacy of rivaroxaban in subjects with recent ACS who received standard of care background aspirin (ASA) therapy without the intention to use thienopyridine therapy (Stratum 1, ASA only) or with the intention to use thienopyridine therapy (Stratum 2; aspirin + thienopyridine). The study was planned for a total duration of 216 days, including a 6-day screening period, 6-month double-blind treatment period, and 1-month follow-up period. The mean treatment duration was 159.1 for pooled rivaroxaban groups and 163.6 days for pooled placebo groups. The sponsor planned to use the results from TIMI 46 to select doses for the TIMI 51 trial.

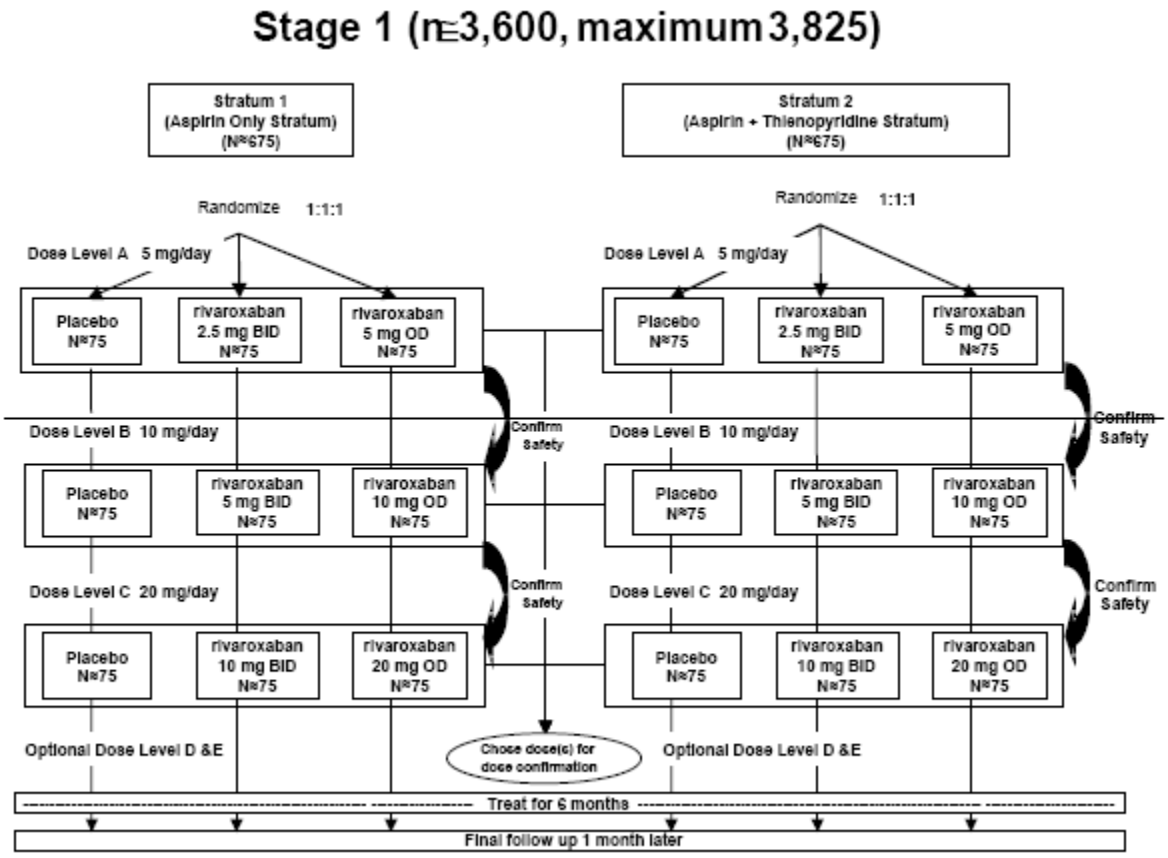
The primary endpoint was a composite of death, MI or repeat myocardial infarction (reMI), stroke (ischemic, hemorrhagic or unknown), or severe recurrent ischemia requiring (SRI) revascularization. The primary safety endpoint was clinically significant bleeding. The key secondary endpoint was a composite of all-cause death, MI (or reMI), or stroke (ischemic, hemorrhagic, or unknown).

A sequential study design was planned, as shown in Figure 14, but Stage 2 was never used, as sample size for Stage 1 was increased to approximately 3500 subjects. Initially, rivaroxaban at a total daily dose (TDD) of 5 mg was tested using qd and bid regimens. An unblinded Operations Committee (OC) reviewed safety and efficacy and on their recommendation increased dosing to total daily doses of 10 and 20 mg. At the discretion of the OC, additional TDD panels of 15 and 30 mg could be tested.

To perform a pooled analysis of TIMI 46 and TIMI 51, the sponsor used a primary endpoint of the composite of CV death, MI, and stroke and not the originally specified primary endpoint from TIMI 46.

The TIMI 46 results are displayed in Table 24. In Stratum 1, there were 77 subjects on rivaroxaban 2.5 mg BID. For rivaroxaban 2.5 mg BID, the hazard ratio shows numerical reductions for the primary composite endpoint of CV death, MI, or stroke but numerical increases for CV death and stroke. For rivaroxaban 5 mg BID, there are numerical reductions in the hazard ratio for the primary endpoint and numerical reductions in CV death and MI, but numerical increases in stroke.

Figure 14. TIMI 46 Study Design



Clinical Study Report, Figure 1, page 35.

Table 24. Sponsor's Analysis: Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, or Stroke) as Adjudicated by the CEC (mITT) (TIMI 46)

	---------- Rivaroxaban ----------									
Subject Stratum	2.5 mg BID (N=153)	5 mg BID (N=527)	All Doses (N=2331)	Placebo (N=1160)	-- 2.5 mg BID vs. Placebo --	Log-Rank	--- 5 mg BID vs. Placebo --	Log-Rank	-- All Doses vs. Placebo -	Log-Rank
Parameter	n(%)	n(%)	n(%)	n(%)	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
All Strata	153	527	2331	1160						
Primary	6(3.9)	14(2.7)	83(3.6)	58(5.0)	0.52 (0.22,1.22)	0.124	0.58 (0.33,1.05)	0.068	0.73 (0.52,1.02)	0.066
CV_Dth	3(2.0)	2(0.4)	24(1.0)	13(1.1)	1.26 (0.35,4.58)	0.727	0.36 (0.08,1.61)	0.165	0.93 (0.48,1.83)	0.842
MI	3(2.0)	12(2.3)	65(2.8)	42(3.6)	0.35 (0.11,1.15)	0.072	0.70 (0.37,1.33)	0.274	0.80 (0.54,1.18)	0.251
Stroke	1(0.7)	1(0.2)	6(0.3)	5(0.4)	1.08 (0.12,9.77)	0.945	0.48 (0.06,4.10)	0.491	0.61 (0.18,1.98)	0.402
ASA	77	97	508	253						
Primary	5(6.5)	6(6.2)	31(6.1)	29(11.5)	0.55 (0.21,1.42)	0.207	0.55 (0.23,1.32)	0.173	0.53 (0.32,0.88)	0.013
CV_Dth	2(2.6)	1(1.0)	11(2.2)	6(2.4)	1.09 (0.22,5.39)	0.919	0.44 (0.05,3.69)	0.440	0.93 (0.34,2.51)	0.882
MI	2(2.6)	5(5.2)	21(4.1)	22(8.7)	0.29 (0.07,1.22)	0.072	0.60 (0.23,1.59)	0.302	0.47 (0.26,0.86)	0.012
Stroke	1(1.3)	1(1.0)	4(0.8)	2(0.8)	1.63 (0.15,17.95)	0.688	1.34 (0.12,14.83)	0.808	1.01 (0.19,5.54)	0.987
ASA + Thieno	76	430	1823	907						
Primary	1(1.3)	8(1.9)	52(2.9)	29(3.2)	0.42 (0.06,3.06)	0.374	0.62 (0.28,1.35)	0.222	0.94 (0.59,1.49)	0.785
CV_Dth	1(1.3)	1(0.2)	13(0.7)	7(0.8)	1.68 (0.21,13.64)	0.624	0.31 (0.04,2.50)	0.242	0.94 (0.37,2.35)	0.893
MI	1(1.3)	7(1.6)	44(2.4)	20(2.2)	0.61 (0.08,4.58)	0.630	0.79 (0.33,1.89)	0.603	1.17 (0.68,2.01)	0.565
Stroke	0	0	2(0.1)	3(0.3)		0.614		0.237	0.33 (0.06,2.00)	0.207

Note: The data shown are for all randomized subjects and the endpoints occurring up to the completion of treatment phase plus 2 days, or 30 days following early discontinuation, or 30 days following randomization for subjects who were randomized but not treated.
Note: A subject could have more than one component event.
Note: n = number of subjects with events; N = number of subjects at risk; % = 100 * n / N.
Note: CV_Dth: Cardiovascular death including unknown death.
Note: HR (95% CI): Hazard ratios (95% confidence interval) as compared to placebo arm are based on the (stratified, only for all strata) Cox proportional hazards model.
Note: Log-Rank P-value: P-values (two-sided) as compared to placebo arm are based on the (stratified, only for all strata) log rank test.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; MI = Myocardial infarction.
Note: All Doses = Riva 2.5, 5, 7.5 (ASA+Thieno only), 10 mg BID and Riva 5, 10, 15 (ASA+Thieno only), 20 mg OD for study 39039039ACS2001.
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Integrated Summary of Efficacy, Table 10, page 61.

6.1.4.5.2 Stratum 1 (ATLAS)

If we now consider the Stratum 1 results from ATLAS, displayed in Table 25 (N = 349 on rivaroxaban 2.5 mg BID), we again see numerical increases in the hazard ratio for CV death on rivaroxaban 2.5 mg BID (and all-cause death, for that matter) while seeing numerical reductions in the primary endpoint. On 5 mg BID, we see numerical reductions in the hazard ratio for the primary endpoint, CV death, death, and MI but numerical increases in stroke. Given this small subgroup on rivaroxaban 2.5 mg BID (N = 426), I think data are insufficient to determine whether rivaroxaban 2.5 mg BID would be beneficial in Stratum 1 type patients. The results actually suggest that for Stratum 1, rivaroxaban 5 mg BID may be the correct dose. The other alternative is that maybe these ACS subjects do not need rivaroxaban at all and should just be treated with a $P2Y_{12}$ inhibitor in addition to their aspirin. These subgroups are too small for any definitive conclusions.

Table 25. Sponsor's Analysis: Effect of Rivaroxaban Compared with Placebo on Primary Efficacy Endpoint and Secondary Efficacy Endpoint 1 and Components as Adjudicated by the CEC (mITT Excluding Sites 091001, 091019, and 091026) (ATLAS)

	Rivaroxaban								-- 2.5 mg BID --	--- 5 mg BID ---	--- Combined ---
	----- 2.5 mg BID ----		------ 5 mg BID -----		------ Combined ------		------ Placebo ------		------ vs. -----	------ vs. -----	------ vs. -----
Subject Stratum	(N=5114)	Event Rate	(N=5115)	Event Rate	(N=10229)	Event Rate	(N=5113)	Event Rate	---- Placebo ---	---- Placebo ---	---- Placebo ---
Parameter	n(%)	(100 pt-yr)	n(%)	(100 pt-yr)	n(%)	(100 pt-yr)	n(%)	(100 pt-yr)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All Strata	5114		5115		10229		5113				
Primary	313(6.1)	5.92	313(6.1)	6.03	626(6.1)	5.97	376(7.4)	7.04	0.84 (0.72,0.97)	0.85 (0.73,0.98)	0.84 (0.74,0.96)
Dth/MI/St	320(6.3)	6.05	321(6.3)	6.18	641(6.3)	6.12	386(7.5)	7.23	0.83 (0.72,0.97)	0.84 (0.73,0.98)	0.84 (0.74,0.95)
CV_Dth	94(1.8)	1.73	132(2.6)	2.49	226(2.2)	2.10	143(2.8)	2.60	0.66 (0.51,0.86)	0.94 (0.75,1.20)	0.80 (0.65,0.99)
Death	103(2.0)	1.90	142(2.8)	2.68	245(2.4)	2.28	153(3.0)	2.78	0.68 (0.53,0.87)	0.95 (0.76,1.19)	0.81 (0.66,1.00)
MI	205(4.0)	3.87	179(3.5)	3.44	384(3.8)	3.66	229(4.5)	4.28	0.90 (0.75,1.09)	0.79 (0.65,0.97)	0.85 (0.72,1.00)
Stroke	46(0.9)	0.85	54(1.1)	1.02	100(1.0)	0.93	41(0.8)	0.75	1.13 (0.74,1.73)	1.34 (0.90,2.02)	1.24 (0.86,1.78)
ASA	349		348		697		353				
Primary	27(7.7)	7.95	24(6.9)	6.90	51(7.3)	7.41	36(10.2)	10.82	0.74 (0.45,1.22)	0.64 (0.38,1.07)	0.69 (0.45,1.05)
Dth/MI/St	28(8.0)	8.24	24(6.9)	6.90	52(7.5)	7.56	36(10.2)	10.82	0.77 (0.47,1.26)	0.64 (0.38,1.07)	0.70 (0.46,1.07)
CV_Dth	12(3.4)	3.41	9(2.6)	2.54	21(3.0)	2.97	10(2.8)	2.84	1.20 (0.52,2.77)	0.89 (0.36,2.20)	1.04 (0.49,2.21)
Death	13(3.7)	3.69	9(2.6)	2.54	22(3.2)	3.11	10(2.8)	2.84	1.30 (0.57,2.96)	0.89 (0.36,2.20)	1.09 (0.52,2.31)
MI	16(4.6)	4.69	10(2.9)	2.85	26(3.7)	3.76	22(6.2)	6.56	0.72 (0.38,1.37)	0.44 (0.21,0.93)	0.58 (0.33,1.02)
Stroke	2(0.6)	0.57	8(2.3)	2.28	10(1.4)	1.42	7(2.0)	2.00	0.28 (0.06,1.37)	1.13 (0.41,3.12)	0.71 (0.27,1.86)
ASA + Thieno	4765		4767		9532		4760				
Primary	286(6.0)	5.78	289(6.1)	5.96	575(6.0)	5.87	340(7.1)	6.79	0.85 (0.72,0.99)	0.87 (0.74,1.01)	0.86 (0.75,0.98)
Dth/MI/St	292(6.1)	5.90	297(6.2)	6.13	589(6.2)	6.01	350(7.4)	6.99	0.84 (0.72,0.98)	0.87 (0.74,1.01)	0.85 (0.75,0.97)
CV_Dth	82(1.7)	1.61	123(2.6)	2.48	205(2.2)	2.04	133(2.8)	2.58	0.62 (0.47,0.82)	0.95 (0.74,1.21)	0.78 (0.63,0.97)
Death	90(1.9)	1.77	133(2.8)	2.69	223(2.3)	2.22	143(3.0)	2.78	0.64 (0.49,0.83)	0.95 (0.75,1.21)	0.79 (0.64,0.98)
MI	189(4.0)	3.81	169(3.5)	3.48	358(3.8)	3.65	207(4.3)	4.13	0.92 (0.75,1.12)	0.83 (0.68,1.02)	0.88 (0.74,1.04)
Stroke	44(0.9)	0.87	46(1.0)	0.93	90(0.9)	0.90	34(0.7)	0.66	1.31 (0.84,2.05)	1.39 (0.89,2.16)	1.35 (0.91,2.00)

Note: The data shown are for all randomized subjects and the endpoint events occuring at or after randomization and the earliest date of the global treatment end date, 30 days after study drug was prematurely discontinued and 30 days after randomization for those subjects who were randomized but not treated.
Note: A subject could have more than one component event.
Note: n = number of subjects with events; N = number of subjects at risk; % = 100 * n / N.
Note: Event Rate (100 pt-yr): number of events per 100 patient years of follow up.
Note: Primary: first occurence of cardiovascular death including unknown death, MI, or stroke; CV_Dth: Cardiovascular death including unknown death; Dth/MI/St (Secondary Efficacy Endpoint 1): first occurence of all cause death, MI or stroke; MI: Myocardial infarction.
Note: HR (95% CI): Hazard ratios (95% confidence interval) as compared to placebo arm are based on the (stratified, only for all strata) Cox proportional hazards model.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.
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Source: Clinical Study Report, Table 27, page 153.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoints included

- The composite of all cause death, MI, or stroke
- Net clinical outcome, defined as the composite of CV death, MI, ischemic stroke, or TIMI major bleeding event not associated with CABG surgery
- The composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization
- The composite of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalization

The results for these analyses are displayed in Table 26.

The sponsor prespecified a hierarchical testing strategy in the SAP that allowed further analyses for the secondary efficacy endpoints if the primary efficacy endpoint was significant. As stated in the Statistical Review by Steve Bai, Ph.D., throughout the ACS program, there was no agreement on the sponsor's hierarchical testing strategy. Further, Dr. Bai did not agree with the allowance of the formal testing of the secondary endpoints on rivaroxaban 2.5 mg BID and 5 mg BID doses. Therefore, with respect to the secondary endpoints, descriptive results only are presented for All Strata and Stratum 2.

Table 26. Effect of Rivaroxaban Compared with Placebo on the Secondary Efficacy Endpoints and Components as Adjudicated by the CEC: mITT (Excluding Sites 091001, 091019, and 091026)

Subject Stratum Parameter	Rivaroxaban			Placebo	2.5 mg BID vs. Placebo	5 mg BID vs. Placebo	Combined vs. Placebo
	2.5 mg BID	5 mg BID	Combined				
ALL STRATA	**N = 5114 n (%)**	**N = 5115 n (%)**	**N = 10229 n (%)**	**N = 5113 n (%)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Death, MI, Stroke	320 (6.3)	321 (6.3)	641 (6.3)	386 (7.5)	0.83 (0.72, 0.97)	0.84 (0.73, 0.98)	0.84 (0.74, 0.95)
Net Clinical Outcome	361 (7.0)	366 (7.2)	727 (7.1)	391 (7.6)	0.93 (0.81, 1.07)	0.95 (0.83, 1.10)	0.94 (0.83, 1.06)
CV death/MI/Stroke/ SRIR	437 (8.5)	421 (8.2)	858 (8.4)	481 (9.4)	0.92 (0.80, 1.04)	0.89 (0.78, 1.01)	0.90 (0.81, 1.01)
CV death/MI/Stroke/ SRIH	372 (7.3)	388 (7.6)	760 (7.4)	447 (8.7)	0.84 (0.73, 0.96)	0.88 (0.77, 1.01)	0.86 (0.76, 0.97)
STRATUM 2 (Aspirin + Thienopyridine)	**N = 4765 n (%)**	**N = 4767 n (%)**	**N = 9532 n (%)**	**N = 4760 n (%)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Death, MI, Stroke	292 (6.1)	297 (6.2)	589 (6.2)	350 (7.4)	0.84 (0.72, 0.98)	0.87 (0.74, 1.01)	0.85 (0.75, 0.97)
Net Clinical Outcome	333 (7.0)	341 (7.2)	674 (7.1)	355 (7.5)	0.95 (0.82, 1.10)	0.98 (0.85, 1.14)	0.96 (0.85, 1.10)
CV death/MI/Stroke/ SRIR	406 (8.5)	393 (8.2)	799 (8.4)	442 (9.3)	0.93 (0.81, 1.06)	0.91 (0.79, 1.04)	0.92 (0.82, 1.03)
CV death/MI/Stroke/ SRIH	340 (7.1)	358 (7.5)	698 (7.3)	405 (8.5)	0.85 (0.73, 0.98)	0.90 (0.78, 1.04)	0.87 (0.77, 0.99)

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; mITT: modified intent-to-treat; SRIR: severe recurrent ischemia requiring revascularization; SRIH: severe recurrent ischemia requiring hospitalization
Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

6.1.6 Other Endpoints

6.1.6.1 All-Cause Mortality

Although all-cause mortality was not a prespecified endpoint in ATLAS, the Division routinely evaluates this event in clinical trials.

In ATLAS, all-cause mortality was one of the components of the first secondary endpoint, a composite of death, MI, and stroke. Further, compared to placebo, rivaroxaban reduced the occurrence of the primary endpoint, a composite of CV death, MI, and stroke. Treatment differences were largely driven by the reduction in CV death. In ATLAS, CV deaths comprised over 92% (226/245) of all combined rivaroxaban deaths.

The sponsor's late exclusion of three study sites (091001, 091019, and 091026) in the final SAP was critical in the overall interpretation of all-cause mortality results using different analysis sets.

6.1.6.1.1 Sites Excluded from the Sponsor's Efficacy Analyses (091001, 091019, 091026)

On December 21, 2010, the sponsor contacted the Division of Scientific Investigations (DSI) at FDA to inform them of potential good clinical practice issues at Site 091001 (Mangalore, India). Per the sponsor's audit, observations included the site using electrocardiograms (ECGs) as data for multiple patients on multiple dates, missing ECGs and laboratory reports to confirm subject eligibility, ECG tracings lacking date and time entries, discrepancies in dated signatures on the informed consent document, and missing investigational drug product. Since the ATLAS ACS 2 TIMI 51 trial was ongoing, the sponsor indicated that data from this site would be used for safety but not for efficacy analyses. The sponsor expressed similar concerns to DSI with respect to Sites 091026 (Hyderabad, India) and 91019 (Bangalore, India) on April 19, 2011 and August 25, 2011, respectively,

At the pre-NDA meeting with the Division of Cardiovascular and Renal Products on May 10, 2011, the sponsor proposed to exclude subjects enrolled at Site 091001 for all efficacy analyses due to potential trial misconduct. However, these data would be included in the safety analyses. While the Division agreed with this approach, when the sponsor explained that they would like to amend the SAP to document this decision for completeness, the Division stated that "late changes to the SAP [were] problematic, but capturing this type of change [was reasonable]. Dr. Stockbridge added that the SAP would need to be very explicit that this was the only change and what impact it would have on the final analysis."

On September 15, 2011, four days prior to the final patient contact on September 19, 2011 and nine days prior to database lock on September 24, 2011, the sponsor submitted the final SAP. In this SAP, the sponsor proposed to exclude a total of three Indian sites, including Sites 091001, 091019, and 091026. FDA Biometrics review of this SAP stated that "making late changes to the SAP [were] problematic and [could] impact the interpretation of the study results." Therefore, sensitivity analyses including/excluding these sites would be conducted.

A total of 198 subjects were screened and 184 subjects were randomized at these sites, including 91 subjects at Site 091001, 54 subjects at Site 091026, and 39 subjects at Site 091019. Excluding these sites would leave 15,342 subjects randomized instead of the original 15,526 subjects.

Twenty-two efficacy events occurred at these three study sites, including 10 primary endpoint events and 1 non-CV death, as summarized below:

Stratum 1:
Placebo:
1 Severe Recurrent Ischemia Requiring Hospitalization

Stratum 2:
Placebo:
2 CV Deaths
1 Severe Recurrent Ischemia Requiring Revascularization
2 Other Cardiac Ischemic Events

Rivaroxaban 2.5 mg BID:
1 CV Death
1 MI
1 Other Cardiac Ischemic Event

Rivaroxaban 5 mg BID:
4 CV Deaths
1 Non-CV Death
2 MIs
3 Severe Recurrent Ischemia Requiring Hospitalization
3 Other Cardiac Ischemic Events

In summary, these 22 events included

- 7 CV Deaths
- 1 Non-CV Death
- 3 MIs
- 5 Severe Recurrent Ischemia Requiring Hospitalization
- 6 Other Cardiac Ischemic Events

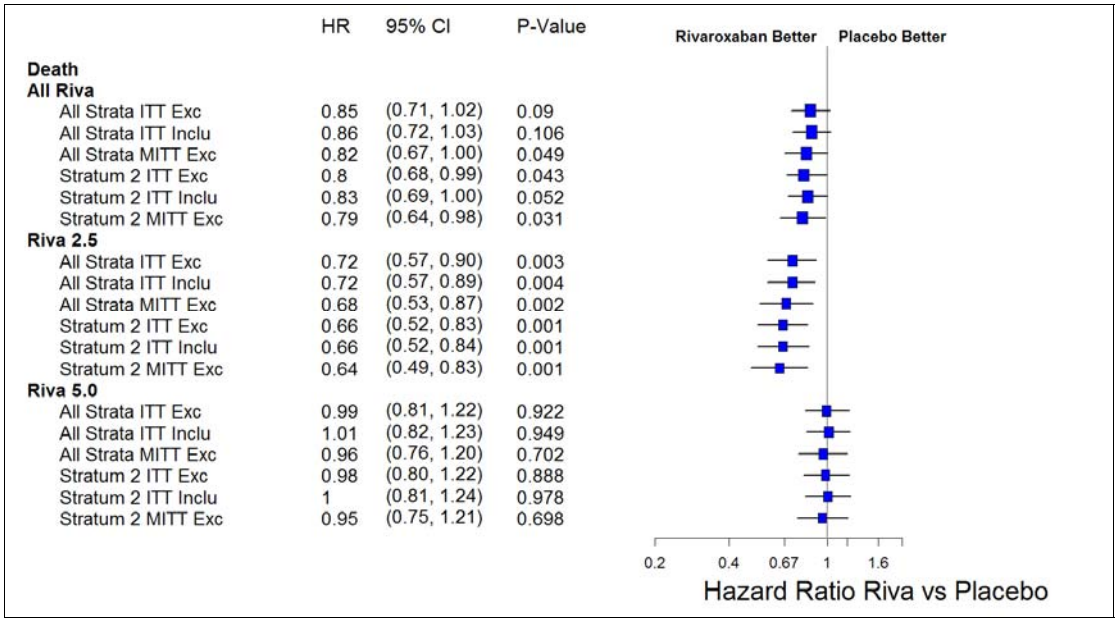
I reviewed the primary endpoint results along with the non-CV death. In all cases, there were data sufficient to adjudicate these events. Therefore, although these sites may have experienced issues with appropriate documentation and oversight of the trial, serious concerns for any clinical trial, these primary endpoint events occurred.

As a result, we include these three sites in most of our sensitivity analyses. For full details about these events, please see Attachment 4.

6.1.6.1.2 All-Cause Mortality Findings in ATLAS

All-cause mortality findings in ATLAS are displayed in Figure 15. All-cause mortality was evaluated using different analysis sets and including/excluding sites 091001, 091019, and 091026. In All Strata, the borderline mortality benefit seen in the mITT analysis set (excluding 3 sites) with p = 0.049 became even more borderline when the mITT analysis included these sites (p = 0.055). These mITT results disappeared in the ITT analyses including and excluding these sites. Although results for rivaroxaban 2.5 mg BID in All Strata and Stratum 2 were robust regardless of the analysis set or site inclusion/exclusion, rivaroxaban 5 mg BID offset the benefit seen with the lower dose. Therefore, the benefit of the combined rivaroxaban doses in the reduction of all-cause mortality is neither strong nor robust and does not warrant a mortality claim.

Figure 15. All-Cause Mortality in ATLAS



Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

6.1.6.2 Stroke

All-cause stroke was a component of the primary endpoint. The effect of rivaroxaban on ischemic stroke was neutral and on hemorrhagic stroke was adverse. Relatively few strokes were adjudicated as uncertain in All Strata and Stratum 2, as displayed in Table 27 and Table 28. In Stratum 2, rivaroxaban 2.5 mg BID demonstrated a 3-fold increase in hemorrhagic stroke and an 18 percent increased risk of fatal stroke.

The sponsor conducted a post hoc analysis to evaluate disability following a stroke event. Scores of 0-2 on a Modified Rankin Scale were classified as causing either no symptoms or slight disability while scores of 3 to 6 were consistent with disabling or fatal strokes. The Modified Rankin Scale is displayed below. In All Strata, these evaluations were not performed in approximately 10% of the rivaroxaban treatment groups and approximately 7% of the placebo treatment group. Approximately 75.0% of subjects in the rivaroxaban 2.5 mg BID All Strata group had no symptoms to slight disability, compared to 46.2% of subjects in the rivaroxaban 5 mg BID treatment group and 47.7% of subjects in the placebo group. The remainder had severe disability or death. Overall, the highest percentage of severe disabling or fatal strokes occurred in the rivaroxaban 5 mg BID treatment group (44.6% in All Strata), and the rate was highest in Stratum 1 (62.5%).

Modified Rankin Scale

Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Reviewer Comments: *This post-hoc analysis does not provide an adequate assessment of disability related to stroke in ATLAS. Ideally, a Modified Rankin Scale should be used to document disability of all subjects at the beginning of the trial and should also be used approximately 3 months following a stroke to assess disability related to the stroke. Therefore, the data presented in this post-hoc analysis are not likely to reflect the true degree of disability patients could expect with a stroke on rivaroxaban, even on the 2.5 mg BID dose.*

As shown in Table 29, subjects with a history of prior ischemic stroke, prior TIA, or prior ischemic stroke/TIA had an increased risk of experiencing a primary endpoint event, driven by increases in CV death, MI, and hemorrhagic stroke. As a result, the use of rivaroxaban should be contraindicated in these patients.

Table 27. Effect of Rivaroxaban Compared with Placebo on Stroke and its Components as Adjudicated by the CEC for All Strata: mITT (Excluding Sites 091001, 091019, and 026)

Stratum	Rivaroxaban			Placebo	2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID	5 mg BID	Combined							
ALL STRATA	N = 5174 n (%)	N = 5176 n (%)	N = 10350 n (%)	N = 5176 n (%)	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Stroke	46 (0.9)	54 (1.1)	100 (1.0)	41 (0.8)	1.13 (0.74, 1.73)	0.562	1.35 (0.90, 2.03)	0.147	1.24 (0.86, 1.79)	0.244
Ischemic Stroke	30 (0.6)	35 (0.7)	65 (0.6)	34 (0.7)	0.89 (0.55, 1.46)	0.644	1.05 (0.66, 1.69)	0.83	0.97 (0.64, 1.47)	0.892
Hemorrhagic Stroke	14 (0.3)	18* (0.4)	32 (0.3)	5 (0.1)	2.83 (1.02, 7.86)	0.046	3.71 (1.38, 9.99)	0.01	3.27 (1.27, 8.38)	0.014
Uncertain Stroke	2 (0.0)	1 (0.0)	3 (0.0)	2 (0.0)	1.00 (0.14, 7.12)	0.998	0.51 (0.05, 5.61)	0.581	0.76 (0.13, 4.55)	0.763

***Includes 4 subdural hematomas**
CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; mITT: modified intent-to-treat
Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

Table 28. Effect of Rivaroxaban Compared with Placebo on Stroke and its Components as Adjudicated by the CEC for Stratum 2: mITT (Excluding Sites 091001, 091019, and 091026)

Stratum	Rivaroxaban			Placebo	2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID	5 mg BID	Combined							
STRATUM 2 (Aspirin + Thienopyridine)	N = 4765 n (%)	N = 4767 n (%)	N = 9532 n (%)	N = 4760 n (%)	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Stroke	44 (0.9)	46 (1.0)	90 (0.9)	34 (0.7)	1.31 (0.84, 2.05)	0.238	1.39 (0.89, 2.16)	0.144	1.35 (0.91, 2.00)	0.137
Ischemic Stroke	29 (0.6)	30 (0.6)	59 (0.6)	28 (0.6)	1.05 (0.62, 1.76)	0.86	1.10 (0.66, 1.85)	0.72	1.07 (0.69, 1.71)	0.76
Hemorrhagic Stroke	13 (0.3)	16 (0.3)	29 (0.3)	5 (0.1)	2.63 (0.99, 8.20)	0.05	3.31 (1.29, 10.11)	0.01	2.97 (1.25, 8.72)	0.01
Uncertain Stroke	2 (0.04)	0	2 (0.02)	1 (0.02)	2.00 (0.19, 43.2)	0.56	1.57e-6 (0, 6.0)	0.24	1.01 (0.1, 21.81)	0.99
Nonfatal Stroke	37 (0.8)	35 (0.7)	72 (0.8)	28 (0.6)	1.34 (0.82, 2.20)	0.24	1.29 (0.78, 2.13)	0.32	1.31 (0.86, 2.06)	0.22
Fatal Stroke	7 (0.1)	11 (0.2)	18 (0.2)	6 (0.1)	1.18 (0.39, 3.66)	0.77	1.89 (0.72, 5.49)	0.2	1.53 (0.64, 4.22)	0.35

Source: Karen A. Hicks, M.D. and Steve Bai, Ph.D., FDA

Table 29. Effect of Rivaroxaban on the Primary Endpoint and its Components in Patients with a Prior History of Ischemic Stroke and/or Transient Ischemic Attack as Adjudicated by the CEC: mITT (Excluding Sites 091001, 091019, and 091026)

ALL STRATA Parameter	Rivaroxaban			Placebo	2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID	5 mg BID	Combined							
Prior Ischemic Stroke	**N = 100 n (%)**	**N = 98 n (%)**	**N = 198 n (%)**	**N = 87 n (%)**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Primary Endpoint	14 (14.0)	12 (12.2)	26 (13.1)	6 (6.9)	1.86 (0.71, 4.85)	0.205	1.76 (0.66, 4.69)	0.0259	1.82 (0.75, 4.43)	0.187
CV death	4 (4.0)	3 (3.1)	7 (3.5)	2 (2.3)	1.50 (0.27, 8.23)	0.64	1.20 (0.20, 7.25)	0.842	1.42 (0.29, 6.84)	0.664
MI	11 (11.0)	5 (5.1)	16 (8.1)	1 (1.1)	8.67 (1.12, 67.28)	0.039	4.50 (0.53, 38.55)	0.17	6.64 (0.88, 50.15)	0.066
Stroke	1 (1.0)	4 (4.1)	5 (2.5)	3 (3.4)	0.27 (0.03, 2.61)	0.259	1.18 (0.26, 5.29)	0.826	0.70 (0.17, 2.94)	0.628
Ischemic Stroke	1 (1.0)	3 (3.1)	4 (2.0)	3 (3.4)	0.27 (0.03, 2.61)	0.259	0.90 (0.18, 4.47)	0.899	0.57 (0.13, 2.54)	0.459
Hemorrhagic Stroke	0 (0.0)	1 (1.0)	1 (0.5)	0 (0.0)	0.998 (,)	-	243E5 (0.00,)	0.998	152E5 (0.00,)	0.998
Uncertain Stroke	-	-	-	-	-					
Prior TIA	**42**	**51**	**93**	**47**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Primary Endpoint	4 (9.5)	1 (2.0)	5 (5.4)	4 (8.5)	1.17 (0.29, 4.70)	0.82	0.22 (0.03, 2.01)	0.182	0.64 (0.17, 2.37)	0.499
CV death	3 (7.1)	1 (2.0)	4 (4.3)	2 (4.3)	1.74 (0.29, 10.43)	0.543	0.45 (0.04, 5.02)	0.52	1.01 (0.19, 5.54)	0.986
MI	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0.00 (0.00,)	0.998	(0.00 (0.00,)	0.997	0.00 (0.00,)	0.998
Stroke	2 (4.8)	0 (0.0)	2 (2.2)	1 (2.1)	2.42 (0.22, 26.71)	0.47	0.00 (0.00,)	0.997	1.06 (0.10, 11.66)	0.964
Ischemic Stroke	1 (2.4)	0 (0.0)	1 (1.1)	1 (2.1)	1.18 (0.07, 18.87)	0.907	0.00 (0.00,)	0.997	0.52 (0.03, 8.26)	0.641
Hemorrhagic Stroke	1 (2.4)	0 (0.0)	1 (1.1)	0 (0.0)	373E5 (0.00,)	0.997	0.997 (,)		183E5 (0.00,)	0.998
Uncertain Stroke	-	-	-	-						

ALL STRATA Parameter	Rivaroxaban			Placebo	2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID	5 mg BID	Combined							
Prior Ischemic Stroke or TIA	**139**	**145**	**284**	**131**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Primary Endpoint	18 (12.9)	13 (9.0)	31 (10.9)	9 (6.9)	1.84 (0.82, 4.09)	0.137	1.28 (0.55, 2.99)	0.572	1.55 (0.74, 3.27)	0.244
CV death	7 (5.0)	4 (2.8)	11 (3.9)	3 (2.3)	2.09 (0.54, 8.10)	0.285	1.14 (0.25, 5.12)	0.863	1.65 (0.46, 5.91)	0.445
MI	11 (7.9)	5 (3.4)	16 (5.6)	2 (1.5)	4.93 (1.09, 22.30)	0.038	2.23 (0.43, 11.51)	0.337	3.55 (0.81, 15.44)	0.092
Stroke	3 (2.2)	4 (2.8)	7 (2.5)	4 (3.1)	0.70 (0.16, 3.11)	0.636	0.89 (0.22, 3.58)	0.875	0.80 (0.23, 2.72)	0.717
Ischemic Stroke	2 (1.4)	3 (2.1)	5 (1.8)	4 (3.1)	0.46 (0.08, 2.53)	0.375	0.67 (0.15, 3.01)	0.604	0.57 (0.15, 2.12)	0.402
Hemorrhagic Stroke	1 (0.7)	1 (0.7)	2 (0.7)	0 (0.0)	275E5 (0.00,)	0.997	262E5 (0.00,)	0.998	164E5 (0.00,)	0.997
Uncertain Stroke	-	-	-	-						

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; mITT: modified intent-to-treat; TIA: transient ischemic attack
Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

6.1.6.3 Net Clinical Outcome

Net clinical outcome, defined as the composite of CV death, MI, ischemic stroke, or non-CABG TIMI major bleeding event, was one of the secondary endpoints. The results for net clinical outcome and its components are displayed in Table 30. In All Strata, there were minimally favorable reductions in hazard ratios for net clinical benefit on rivaroxaban combined, rivaroxaban 2.5 mg BID, and rivaroxaban 5 mg BID, but none of these reductions achieved "statistical significance"[3] compared to placebo. On rivaroxaban combined, the "statistically significant" reductions in CV death and MI were offset by a 3.4-fold increase in Non-CABG-Related TIMI Major Bleeding.

In All Strata, the greatest reduction in hazard ratio occurred for CV death on rivaroxaban 2.5 mg BID and for MI on rivaroxaban 5 mg BID. There was a dose-dependent escalation in Non-CABG-Related TIMI Major Bleeding, marked by a 3-fold increase on rivaroxaban 2.5 mg BID and a 3.8-fold increase on rivaroxaban 5 mg BID. Once again, virtually all possible benefit was offset by bleeding risk. Results were similar for Stratum 2.

[3]Please note that FDA has provided descriptive statistics only for the secondary endpoints in Table 26. The term "statistical significance" is used in the discussion above to highlight the degree of reductions in hazard ratios for components of net clinical outcome.

Table 30. Sponsor's Analysis: Effect of Rivaroxaban Compared with Placebo on Net Clinical Outcome and its Components as Adjudicated by the CEC: mITT (Excluding Sites 091001, 091019, and 091026)

Subject Stratum Parameter	Rivaroxaban			Placebo	2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID	5 mg BID	Combined							
ALL STRATA	**N = 5114 n (%)**	**N = 5115 n (%)**	**N = 10229 n (%)**	**N = 5113 n (%)**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Net Clinical Outcome	361 (7.1)	366 (7.2)	727 (7.1)	391 (7.6)	0.93 (0.81, 1.07)	0.320	0.95 (0.83, 1.10)	0.508	0.94 (0.83, 1.06)	0.337
CV Death	94 (1.8)	132 (2.6)	226 (2.2)	143 (2.8)	0.66 (0.51, 0.86)	0.002	0.94 (0.75, 1.20)	0.633	0.80 (0.65, 0.99)	0.038
MI	205 (4.0)	179 (3.5)	384 (3.8)	229 (4.5)	0.90 (0.75, 1.09)	0.270	0.79 (0.65, 0.97)	0.020	0.85 (0.72, 1.00)	0.047
Ischemic Stroke	30 (0.6)	35 (0.7)	65 (0.6)	34 (0.7)	0.89 (0.55, 1.45)	0.643	1.05 (0.65, 1.68)	0.844	0.97 (0.64, 1.47)	0.886
Non-CABG TIMI Major	68 (1.3)	85 (1.7)	153 (1.5)	23 (0.4)	2.99 (1.86, 4.80)	<0.001	3.81 (2.40, 6.04)	<0.001	3.40 (2.19, 5.26)	<0.001
STRATUM 2 (Aspirin + Thienopyridine)	**N = 4765 n (%)**	**N = 4767 n (%)**	**N = 9532 n (%)**	**N = 4760 n (%)**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Net Clinical Outcome	333 (7.0)	341 (7.2)	674 (7.1)	355 (7.5)	0.95 (0.82, 1.10)	0.473	0.98 (0.85, 1.14)	0.818	0.96 (0.85, 1.10)	0.585
CV Death	82 (1.7)	123 (2.6)	205 (2.2)	133 (2.8)	0.62 (0.47, 0.82)	<0.001	0.95 (0.74, 1.21)	0.669	0.78 (0.63, 0.97)	0.028
MI	189 (4.0)	169 (3.5)	358 (3.8)	207 (4.3)	0.92 (0.75, 1.12)	0.401	0.83 (0.68, 1.02)	0.077	0.88 (0.74, 1.04)	0.131
Ischemic Stroke	29 (0.6)	30 (0.6)	59 (0.6)	28 (0.6)	1.05 (0.62, 1.76)	0.864	1.10 (0.66, 1.84)	0.723	1.07 (0.68, 1.68)	0.760
Non-CABG TIMI Major	66 (1.4)	81 (1.7)	147 (1.5)	23 (0.5)	2.90 (1.81, 4.67)	<0.001	3.64 (2.29, 5.78)	<0.001	3.27 (2.10, 5.07)	<0.001

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; mITT: modified intent-to-treat
Analysis verified by Steve Bai, Ph.D., Division of Biometrics I, FDA

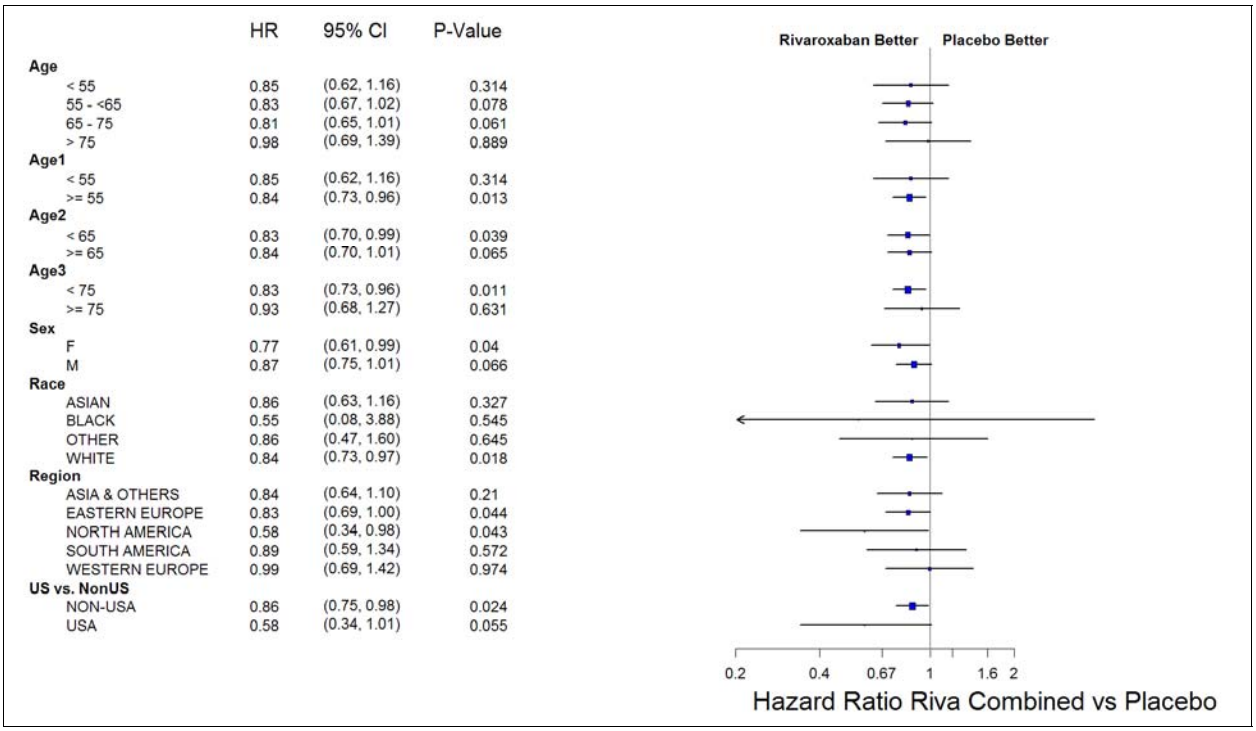
6.1.7 Subpopulations

6.1.7.1 Age, Sex, Ethnicity

We conducted subgroup analyses to evaluate the effectiveness of rivaroxaban in different populations. Using the mITT analysis set in All Strata, most age, sex, and ethnic subgroups had favorable hazard ratios with rivaroxaban, compared with placebo, as shown in Table 27.

In subjects > 75 and ≥ 75, however, the hazard ratios approached or exceeded 1. When these data are taken into consideration with the bleeding results, it is apparent that bleeding risk in this subgroup is markedly increased while efficacy is unclear.

Figure 16. Hazard Ratios of the Primary Efficacy Endpoint by Age, Sex, and Race for Combined Rivaroxaban Compared with Placebo in All Strata: mITT (Excluding Sites 091001, 091019, and 091026)



Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

With respect to the primary endpoint, there were no dose-dependent increases in effectiveness with rivaroxaban in these subgroups, except for possibly the 55 - < 65 year old age group.

Figure 17. Hazard Ratios of the Primary Efficacy Endpoint by Age, Sex, and Race for Rivaroxaban 2.5 mg Compared with Placebo in All Strata: mITT (Excluding Sites 091001, 091019, and 091026)

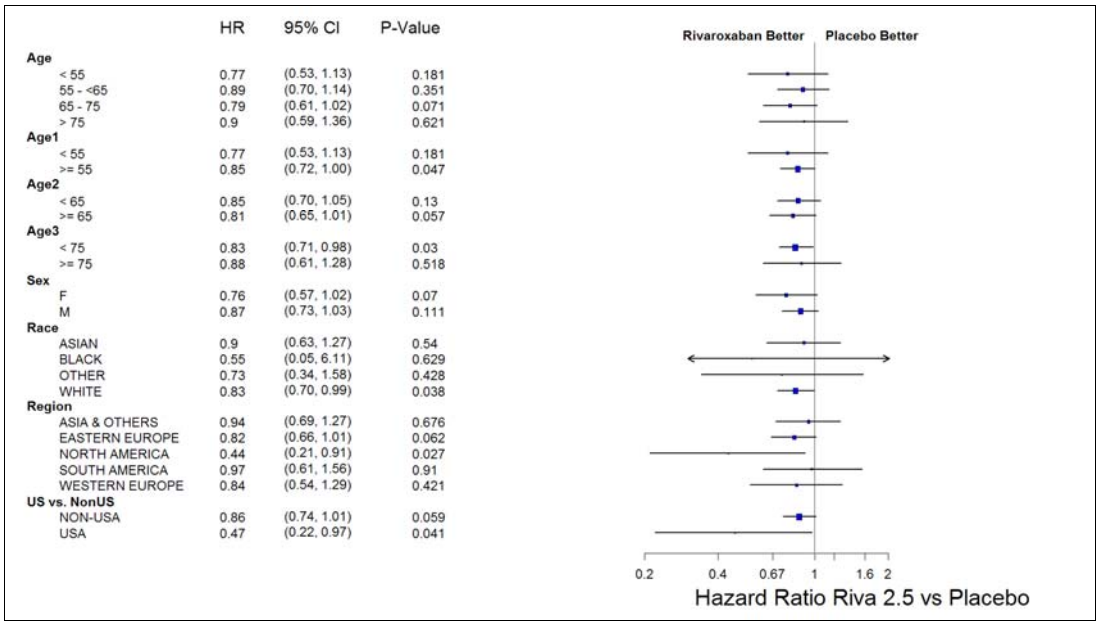
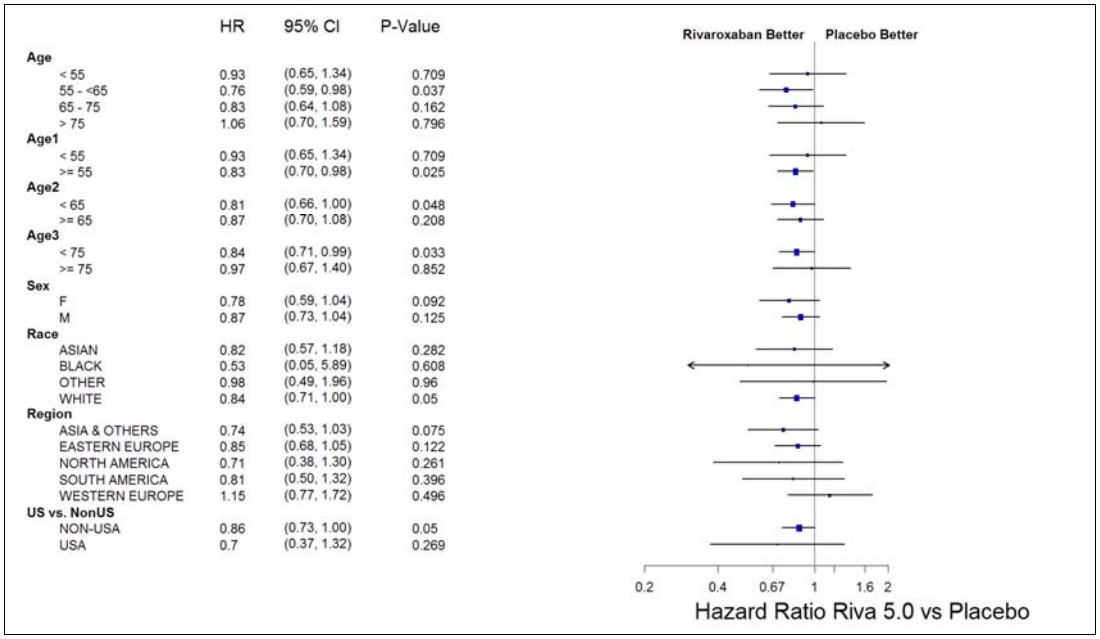


Figure 18. Hazard Ratios of the Primary Efficacy Endpoint by Age, Sex, and Race for Rivaroxaban 5 mg Compared with Placebo in All Strata: mITT (Excluding Sites 091001, 091019, and 091026)



Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In ATLAS, there was no apparent dose-dependent increase in effectiveness with rivaroxaban (5 mg BID versus 2.5 mg BID).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Rivaroxaban has a terminal elimination half-life of 5 to 9 hours in healthy subjects aged 20 to 45 years and 11-13 hours in the elderly. Efficacy would not be expected to persist beyond 5 terminal half-lives. There did not appear to be tolerance issues with rivaroxaban.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Revascularization at Index Event or During Study

In a subgroup analysis, rivaroxaban appeared to be most beneficial in subjects who did not undergo percutaneous coronary intervention or CABG at the time of the index event and in subjects who underwent PCI or CABG during the course of the study, as shown in Table 31.

Table 31. Effect of Rivaroxaban Compared with Placebo on the Primary Endpoint in Subjects who Underwent Index PCI or Index CABG or in Subjects who Underwent PCI or CABG during Study: mITT, Excluding 3 sites (ALL STRATA)

ALL STRATA Parameter	Rivaroxaban			Placebo	2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID	5 mg BID	Combined		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Index PCI										
No	160/2000	172/2013	332/4013	211/2017	0.75 (0.61, 0.93)	0.007	0.81 (0.66, 0.99)	0.040	0.78 (0.66, 0.93)	0.005
Yes	153/3114	141/3101	294/6215	165/3096	0.94 (0.75, 1.17)	0.579	0.88 (0.70, 1.10)	0.269	0.91 (0.75, 1.10)	0.335
Index CABG										
No	312/5093	313/5097	625/10190	374/5088	0.84 (0.72, 0.97)	0.022	0.85 (0.73, 0.99)	0.0344	0.84 (0.74, 0.96)	0.009
Yes	1/21	0/17	1/38	2/25	0.61 (0.06, 6.76)	0.689	0.00 (0.00,)	0.998	0.35 (0.03, 3.90)	0.395
PCI or CABG during Study										
No	184/4329	205/4379	389/8708	228/4353	0.82 (0.68, 1.00)	0.046	0.92 (0.76, 1.11)	0.364	0.87 (0.74, 1.02)	0.090
Yes	129/785	108/736	237/1521	148/760	0.82 (0.65, 1.04)	0.097	0.73 (0.57, 0.94)	0.014	0.78 (0.63, 0.95)	0.016

Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

7 Review of Safety

Safety Summary

1. Rivaroxaban, compared to placebo, increased the risk of all bleeding events.

   - In All Strata, including CABG and Non-CABG-Related bleeding, rivaroxaban 2.5 mg BID significantly increased the risk of
     - TIMI Major bleeding
     - TIMI Major or Minor Bleeding
     - TIMI Life-Threatening bleeding
     - Intracranial Hemorrhage
     - TIMI Minor bleeding
     - TIMI Clinically Significant bleeding
     - TIMI Medical Attention bleeding

     Rivaroxaban 2.5 mg BID did NOT significantly increase the risk of TIMI Major Fatal bleeding or fatal intracranial hemorrhage.

   - In Stratum 2, the most clinically relevant Stratum for U.S. ACS patients, rivaroxaban (2.5 mg BID) significantly increased all
     - TIMI Major or Minor bleeding
     - TIMI Major bleeding
     - TIMI Life-threatening bleeding
     - TIMI Clinically Significant bleeding
     - TIMI Medical Attention bleeding

     Rivaroxaban 2.5 mg BID did NOT significantly increase the risk of TIMI Major Fatal bleeding or fatal intracranial hemorrhage.

   - With respect to Non-CABG-Related bleeding in Stratum 2, rivaroxaban (2.5 mg BID) significantly increased the risk of
     - TIMI Major or Minor bleeding
     - TIMI Major bleeding
     - TIMI Life-Threatening bleeding
     - Intracranial bleeding
     - TIMI Clinically Significant bleeding
     - TIMI Medical Attention bleeding

     Rivaroxaban 2.5 mg BID did NOT significantly increase the risk of TIMI Major Fatal bleeding or fatal intracranial hemorrhage.

- In Stratum 2, rivaroxaban (2.5 mg BID) reduced the rate of the primary endpoint by 15% while increasing the rate of Non-CABG-related bleeding. There was a 2-fold increase in TIMI Major Fatal bleeding and 3-fold increases in TIMI Major bleeding, intracranial hemorrhage, hemorrhagic stroke, TIMI Life-Threatening Bleeding, and TIMI Major or Minor bleeding. There was also an 18% increase in the risk of fatal stroke. Although the hazard ratios were increased, the absolute incidence of these events was low as follows: TIMI Major Fatal bleeding (0.1%); fatal stroke (0.1%), TIMI Major bleeding (1.3%); intracranial hemorrhage (0.3%); hemorrhagic stroke (0.3%); TIMI Life-Threatening Bleeding (0.8%); and TIMI Major or Minor bleeding (2.0%).

2. Rivaroxaban 2.5 mg BID did not significantly increase the risk of CABG-Related TIMI Major or Minor, TIMI Major, TIMI Major Fatal, TIMI Life-Threatening, intracranial hemorrhage, fatal intracranial hemorrhage, Clinically Significant bleeding, or TIMI Medical Attention bleeding.

3. Subjects ≥ 75 years of age and subjects with weight < 60 kg, in particular, had an increased risk of experiencing bleeding events.

4. There was a dose-dependent increase in bleeding events on rivaroxaban.

5. There was a dose-dependent increase in fatal bleeding events on rivaroxaban, especially with respect to intracranial hemorrhage.

6. Compared to other populations (e.g., nonvalvular atrial fibrillation; prophylaxis of deep vein thrombosis), ACS subjects, who were placed on rivaroxaban immediately after the index event and frequently had serum AST, ALT, and total bilirubin elevations before being started on rivaroxaban, appeared to have a more pronounced tendency for liver injury. Therefore, rivaroxaban, even in lower doses than what is recommended for other uses, appears possibly to cause mild liver injury in some patients. This finding likely reflects some increased susceptibility to drug-induced liver injury in patients with ACS.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety review focuses on results of the ATLAS ACS 2 TIMI 51 trial.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In All Strata, the median exposure for rivaroxaban combined was 386 days and for placebo was 399 days. Exposure for All Strata, including any study drug interruption, is summarized in Table 32. Stratum 1 had the lowest median exposure; the median exposure for rivaroxaban combined was 351 days and for placebo was 349 days. For Stratum 2, median exposure for rivaroxaban combined was 388 days and for placebo was 401 days.

Table 32. Total Duration of Treatment (Including Any Study Drug Interruption) (Safety Analysis Set)

ALL STRATA	Rivaroxaban			Placebo	Total
	2.5 mg BID (N=5115)	5 mg BID (N=5110)	Combined (N=10225)	(N=5125)	(N=15350)
Mean	395.8	385.6	390.7	399.9	393.8
SD	233.28	237.28	235.33	232.55	234.44
Median	397.0	376.5	386.0	399.0	390.5
Minimum	1	1	1	1	1
Maximum	927	929	929	932	932
Total Exposure (patient years)	5542.4	5394.8	10937.2	5611.2	16548.5
Cumulative Duration of Treatment, n (%)					
N	**5115**	**5110**	**10225**	**5125**	**15350**
≥ 3 months	4449 (87.0)	4342 (85.0)	8791 (86.0)	4465 (87.1)	13256 (86.4)
≥ 6 months	4054 (79.3)	3942 (77.1)	7996 (78.2)	4109 (80.2)	12105 (78.9)
≥ 12 months	2785 (54.4)	2657 (52.0)	5442 (53.2)	2816 (54.9)	8258 (53.8)
≥ 18 months	1574 (30.8)	1547 (30.3)	3121 (30.5)	1624 (31.7)	4745 (30.9)
≥ 24 months	509 (10.0)	498 (9.7)	1007 (9.8)	508 (9.9)	1515 (9.9)

Total duration of treatment (including days on/off study drug)=date of the last study medication administration – date of the first study medication administration +1. Clinical Study Report, Table 21, page 132.

7.2.1.1 Concomitant Aspirin and Thienopyridine Use

In All Strata, concomitant aspirin use was 99.9% in all treatment groups and concomitant thienopyridine use was 93.6% between the first dose of study drug and the last dose of study drug.

7.2.1.2 Compliance

In All Strata, approximately 94.2 % of subjects had compliance rates ≥ 85%. Approximately 4.5% of subjects had compliance rates from 60 to less than 85%, and 1.3% of subjects had compliance rates < 60%.

Subjects were valid for safety if they had compliance rates ≥ 85% over the course of the trial.

7.2.2 Explorations for Dose Response

There was a dose-dependent increase in bleeding adverse reactions in ATLAS.

Drs. Divya Menon-Andersen and Dhananjay Marathe evaluated exposure outcome relationships in TIMI 46, a phase 2 dose-ranging study. In TIMI 46, clinically significant bleeding was the primary safety endpoint and increased with increasing dose/exposure. There were no dose-dependent trends observed for efficacy, but the study was also not adequately powered to inform efficacy.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See Section 7.3.4, Significant Adverse Events (Bleeding), and Section 7.3.5, Submission Specific Primary Safety Concerns (Liver Injury).

7.3 Major Safety Results

7.3.1 Deaths

In All Strata in the mITT analysis set, there were 94, 132, and 143 CV deaths on rivaroxaban 2.5 mg BID, rivaroxaban 5 mg BID, and placebo, respectively, for a total of 369 CV deaths. With respect to all-cause mortality, there were 103, 142, and 153 deaths on rivaroxaban 2.5 mg BID, rivaroxaban 5 mg BID, and placebo. On rivaroxaban combined, cardiovascular deaths made up 92% of all deaths (226/245). Please see Section 6 for full details. Most of the CV deaths were sudden or unwitnessed death, and these deaths were markedly reduced in the rivaroxaban treatment groups, compared to placebo, as shown in Table 33.

Please see Dr. Marciniak's review with respect to his analysis of death in ATLAS.

Table 33. Summary of Cardiovascular Deaths by Primary Cause as Adjudicated by the CEC (mITT Excluding Sites 091001, 091019, and 091026)

Cardiovascular Mortality	Rivaroxaban			Placebo
	2.5 mg BID (N = 5114) n (%)	5 mg BID (N = 5115) n (%)	Combined (N = 10229) n (%)	(N = 5113) n (%)
Cardiovascular Deaths	**92 (1.8)**	**129 (92.5)**	**221 (2.2)**	**142 (2.8)**
Non-hemorrhagic stroke	1 (< 0.1)	3 (0.1)	4 (< 0.1)	3 (0.1)
Intracranial Hemorrhage	5 (0.1)	6 (0.1)	4 (< 0.1)	3 (0.1)
Atherosclerotic vascular disease (excluding coronary)	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)	1 (< 0.1)
Congestive heart failure/cardiogenic shock	8 (0.2)	19 (0.4)	27 (0.3)	17 (0.3)
Directly related to revascularization (CABG or PCI)	3 (0.1)	2 (< 0.1)	5 (< 0.1)	4 (0.1)
Cardiac arrhythmia	1 (< 0.1)	4 (0.1)	5 (< 0.1)	5 (0.1)
Pulmonary embolism	0	0	0	3 (0.1)
Sudden or unwitnessed death	55 (1.1)	59 (1.2)	114 (1.1)	81 (1.6)
Hemorrhage, not intracranial	0	5 (0.1)	5 (< 0.1)	1 (< 0.1)
Myocardial infarction	18 (0.4)	30 (0.6)	48 (0.5)	23 (0.4)
Other vascular	0	0	0	0
Unknown	**2 (< 0.1)**	**3 (0.1)**	**5 (< 0.1)**	**1 (< 0.1)**

CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention. Source: Clinical Study Report, Table 29, page 167. Analysis verified by Karen A. Hicks, M.D.

In All Strata in the Safety analysis set, there were 118, 161, and 164 CV deaths on rivaroxaban 2.5 mg BID, rivaroxaban 5 mg BID, and placebo, respectively for a total of 443 CV deaths. With respect to all-cause mortality, there were 145, 194, and 193 deaths on rivaroxaban 2.5 mg BID, rivaroxaban 5 mg BID, and placebo, respectively. On rivaroxaban combined, cardiovascular deaths made up 82 % of all deaths (279/339). Non CV deaths were largely related to malignancy, as shown in Table 34.

Table 34. Summary of All-Cause Mortality by Primary Cause as Adjudicated by CEC (Safety Analysis Set) (ATLAS)

All-Cause Mortality	Rivaroxaban			Placebo
	2.5 mg BID (N = 5115) n (%)	5 mg BID (N = 5110) n (%)	Combined (N = 10225) n (%)	(N = 5125) n (%)
Cardiovascular Deaths	**118 (2.3)**	**161 (3.2)**	**279 (2.7)**	**163 (3.2)**
Non-hemorrhagic stroke	2 (< 0.1)	5 (0.1)	7 (0.1)	4 (0.1)
Intracranial Hemorrhage	7 (0.1)	7 (0.1)	14 (0.1)	6 (0.1)
Atherosclerotic vascular disease (excluding coronary)	1 (< 0.1)	3 (0.1)	4 (< 0.1)	1 (< 0.1)
Congestive heart failure/cardiogenic shock	12 (0.2)	27 (0.5)	39 (0.4)	19 (0.4)
Directly related to revascularization (CABG or PCI)	3 (0.1)	2 (< 0.1)	5 (< 0.1)	5 (< 0.1)
Cardiac arrhythmia	1 (< 0.1)	4 (0.1)	5 (< 0.1)	6 (0.1)
Pulmonary embolism	0	0	0	3 (0.1)
Sudden or unwitnessed death	69 (1.3)	74 (1.4)	143 (1.4)	96 (1.9)
Hemorrhage, not intracranial	1 (< 0.1)	5 (0.1)	6 (0.1)	1 (< 0.1)
Myocardial infarction	22 (0.4)	34 (0.7)	56 (0.5)	23 (0.4)
Other vascular	0	0	0	0
Non-Cardiovascular Deaths	**22 (0.4)**	**29 (0.6)**	**51 (0.5)**	**24 (0.5)**
Accidental / trauma	2 (< 0.1)	2 (< 0.1)	4 (< 0.1)	4 (0.1)
Respiratory failure	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)	2 (< 0.1)
Infection	2 (< 0.1)	10 (0.2)	12 (0.1)	2 (< 0.1)
Malignancy	17 (0.3)	13 (0.3)	30 (0.3)	14 (0.3)
Suicide	0	1 (< 0.1)	1 (< 0.1)	1 (< 0.1)
Liver failure	0	0	0	0
Renal failure	0	0	0	1 (< 0.1)
Other non-vascular	0	1 (< 0.1)	1 (< 0.1)	0
Unknown	**5 (0.1)**	**4 (0.1)**	**9 (0.1)**	**5 (0.1)**

CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention
Source: Clinical Study Report, Table 37, page 221.
Analysis verified by Karen A. Hicks, M.D.

7.3.2 Nonfatal Serious Adverse Events

Frequent nonfatal serious adverse events that appeared to be balanced between treatment groups included pneumonia, alanine aminotransferase increased, and atrial fibrillation. There was a dose-dependent increase in gastrointestinal hemorrhage and unstable angina.

7.3.3 Dropouts and/or Discontinuations

Most subjects discontinued study drug permanently due to bleeding events. Of the 1294 subjects who "withdrew consent," 182 subjects had an adverse event (14%). The main reasons subjects discontinued were bleeding (epistaxis, hematuria, gingival bleeding, hematoma, anemia, ecchymosis, hemoptysis, rectal hemorrhage, contusion, gastrointestinal hemorrhage), percutaneous coronary intervention, angina pectoris, angina unstable, alanine aminotransferase increased, dyspnea, ischemic stroke, and pneumonia. Epistaxis, hematuria and gingival bleeding were increased on rivaroxaban, compared to placebo.

	Placebo (N = 51)	**Rivaroxaban 2.5 mg BID (N = 62)**	**Rivaroxaban 5 mg BID (N = 69)**
Epistaxis	3 (5.9%)	7 (11.3%)	10 (14.5%)
Percutaneous Coronary Intervention	3 (5.9)	9 (14.5%)	5 (7.2%)
Hematuria	2 (3.9%)	6 (9.7%)	6 (8.7%)
Gingival Bleeding	1 (2.0%)	4 (6.5%)	6 (8.7%)
Angina Pectoris	4 (7.8%)	5 (8.1%)	1 (1.4%)
Angina Unstable	3 (5.9)	3 (4.8%)	3 (4.3%)
Hematoma	3 (5.9)	2 (3.2%)	3 (4.3%)
Anemia	3 (5.9)	1 (1.6 %)	3 (4.3%)
Ecchymosis	2 (3.9%)	3 (4.8%)	2 (2.9%)
Alanine aminotransferase increased	1 (2.0%)	2 (3.2%)	3 (4.3%)
Dyspnea	2 (3.9%)	1 (1.6%)	3 (4.3%)
Hemoptysis	3 (5.9)	3 (4.8%)	0
Ischemic stroke	4 (7.8%)	1 (1.6%)	1 (1.4%)
Pneumonia	3 (5.9)	2 (3.2%)	1 (1.4%)
Rectal hemorrhage	3 (5.9)	1 (1.6%)	2 (2.9%)
Cardiac failure	1 (2.0%)	3 (4.8%)	1 (1.4%)
Dizziness	2 (3.9%)	1 (1.6%)	2 (2.9%)
Headache	1 (2.0%)	0	4 (5.8%)
Atrial fibrillation	2 (3.9%)	1 (1.6%)	1 (1.4%)

Contusion	2	1	1
Gastrointestinal hemorrhage	2	1	1
ADSL (TRLSTAT, TRTSTAT), ADAE			

7.3.4 Significant Adverse Events – Bleeding

7.3.4.1 Primary Safety Endpoint: Non-CABG-Related TIMI Major Bleeding Events

The primary safety endpoint was Non-CABG-Related TIMI Major bleeding in treatment emergent subjects, defined as those who received at least one dose of study drug and had endpoint events between the first study drug administration and 2 days after the last study drug administration, inclusive. Compared to placebo, there was a dose-dependent increase in the risk of Non-CABG-Related TIMI Major bleeding with rivaroxaban, as shown in Table 35. Results were similar in Stratum 2. Although the hazard ratios were increased, the absolute incidence of these events was low. Kaplan-Meier Curves for All Strata and Stratum 2 for Non-CABG-related bleeding events are displayed in Figure 19 and

Figure 20.

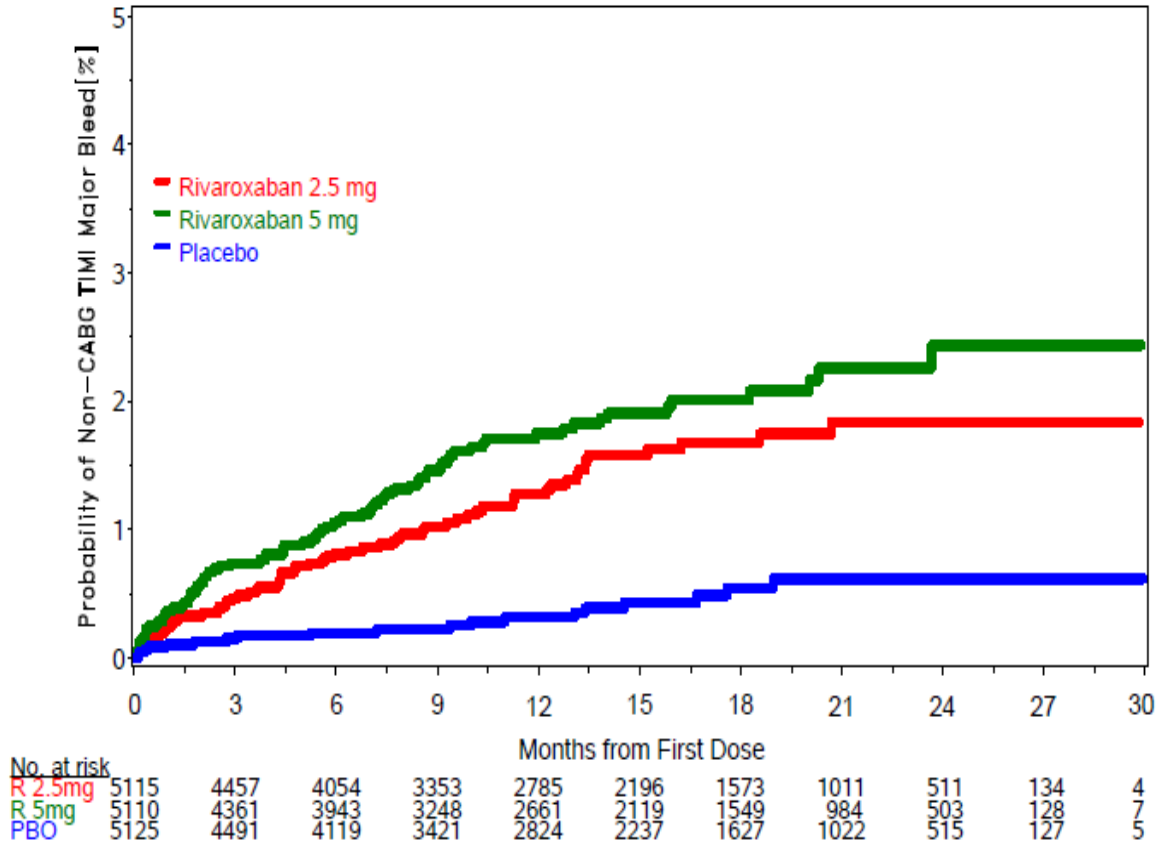
In general, treatment emergent 7-day and 30-day results showed decreasing risks of non-CABG-related bleeding events over time in All Strata on rivarobaban treatment groups compared to placebo (Treatment Emergent 7-Day All Strata: rivaroxaban 2.5 mg BID versus placebo: HR 3.03 and $p < 0.001$; rivaroxaban 5 mg BID versus placebo: HR 3.90 and p-value < 0.001; and rivaroxaban combined: HR 3.46 and p-value < 0.001) (Treatment Emergent 30-Day All Strata: rivaroxaban 2.5 mg BID versus placebo: HR 2.87 and $p < 0.001$; rivaroxaban 5 mg BID versus placebo: HR 3.5 and p-value < 0.001; and rivaroxaban combined: HR 3.19 and p-value < 0.001). Results were similar for Stratum 2.

Table 35. Effect of Rivaroxaban Compared with Placebo on Non-CABG-Related Bleeding as Adjudicated by the CEC (Treatment Emergent + 2 Days)

NCABG TIMI Major Bleeding Events	Rivaroxaban				Placebo						
Strata	**N**	**n**	**(%)**	**Event Rate (100 pt-yr)**	**N**	**n**	**(%)**	**Event Rate (100 pt-yr)**	**HR**	**95% CI**	**Log-Rank p-value**
ALL STRATA											
Rivaroxaban 2.5 mg BID	5115	65	(1.3%)	1.17	5125	19	(0.4%)	0.34	3.46	(2.08, 5.77)	< 0.001
Rivaroxaban 5 mg BID	5110	82	(1.6%)	1.52	5125	19	(0.4%)	0.34	4.47	(2.71, 7.36)	< 0.001
Combined	10225	147	(1.4%)	1.34	5125	19	(0.4%)	0.34	3.96	(2.46, 6.38)	< 0.001
STRATUM 2											
Rivaroxaban 2.5 mg BID	4772	63	(1.3%)	1.21	4773	19	(0.4%)	0.36	3.35	(2.01, 5.60)	< 0.001
Rivaroxaban 5 mg BID	4768	78	(1.6%)	1.55	4773	19	(0.4%)	0.36	4.26	(2.58, 7.03)	< 0.001
Combined	9540	141	(1.5%)	1.38	4773	19	(0.4%)	0.36	3.80	(2.35, 6.14)	< 0.001
STRATUM 1											
Rivaroxaban 2.5 mg BID	343	2	(0.6%)	0.56	352	0					NE
Rivaroxaban 5 mg BID	342	4	(1.2%)	1.11	352	0					NE
Combined	685	6	(0.9%)	0.84	352	0					NE

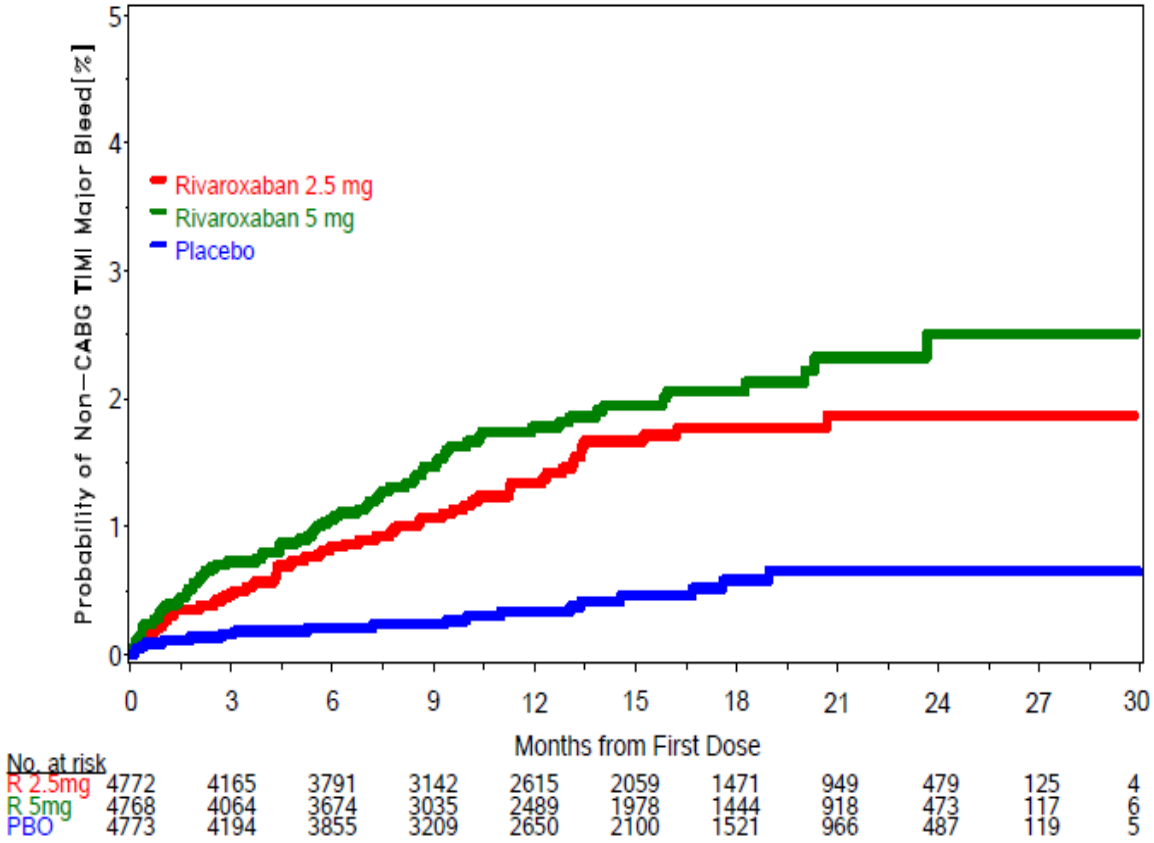
Treatment Emergent Safety Population (events occurring between the first study drug administration and 2 days after the last study drug administration, inclusive).
CI: confidence interval; HR: hazard ratio; NCABG: Non-Coronary Artery Bypass Graft Surgery bleeding.

Figure 19. Time to Non-CABG-Related TIMI Major Bleeding Event (All Strata)



(Source: Karen A. Hicks, M.D. B. Nhi Beasley, Pharm.D.)

Figure 20. Time to Non-CABG-Related TIMI Major Bleeding Event (Stratum 2)



(Source: Karen A. Hicks, M.D. and B. Nhi Beasley, Pharm.D.)

7.3.4.1.1 Subgroup Analysis for the Primary Safety Endpoint

We conducted a number of subgroup analyses with respect to the primary safety endpoint of Non-CABG-Related Bleeding Events. There were dose-dependent increases in bleeding risk for virtually all subgroups, including subjects ≥ 75 and women. Subjects with a history of congestive heart failure at baseline had a reduced risk of bleeding on rivaroxaban 2.5 mg BID compared to placebo but an increased risk of bleeding on rivaroxaban 5 mg BID compared to placebo. Results of these subgroup analyses are displayed in Figure 21 through Figure 26.

Figure 21. Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on Non-CABG-Related TIMI Major Bleeding Events

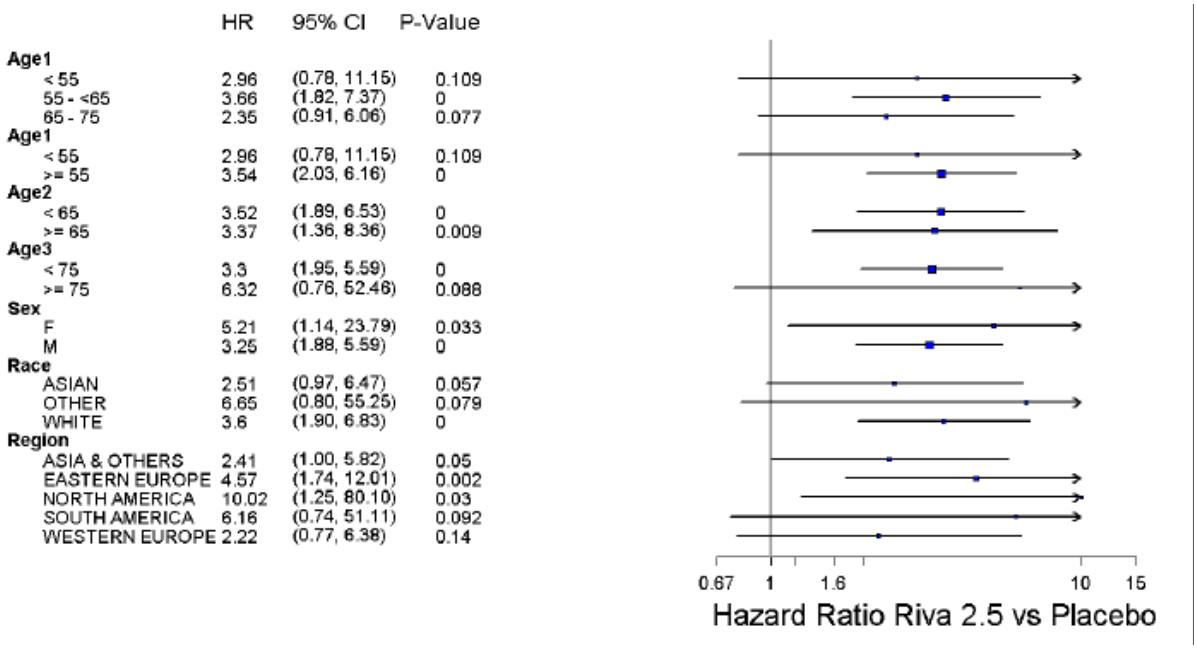
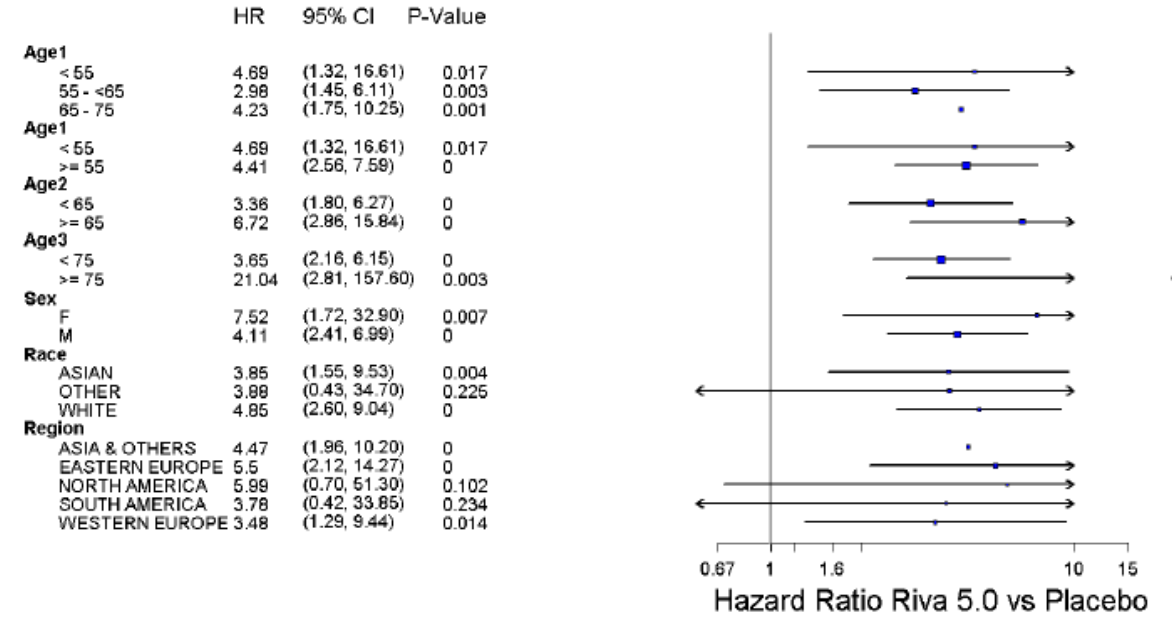


Figure 22. Effect of Rivaroxaban 5 mg BID Compared with Placebo on Non-CABG-Related TIMI Major Bleeding Events



Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

Figure 23. Effect of Combined Rivaroxaban Compared with Placebo on Non-CABG-Related TIMI Major Bleeding Events

	HR	95% CI	P-Value
Age1			
< 55	3.8	(1.13, 12.78)	0.017
55 - <65	3.32	(1.70, 6.45)	0.003
65 - 75	3.29	(1.40, 7.75)	0.001
Age1			
< 55	3.8	(1.13, 12.78)	0.017
>= 55	3.97	(2.36, 6.67)	0
Age2			
< 65	3.44	(1.92, 6.16)	0
>= 65	5.04	(2.18, 11.66)	0
Age3			
< 75	3.47	(2.12, 5.69)	0
>= 75	13.38	(1.81, 98.87)	0.003
Sex			
F	6.39	(1.51, 26.99)	0.007
M	3.67	(2.21, 6.09)	0
Race			
ASIAN	3.14	(1.32, 7.46)	0.004
OTHER	5.17	(0.66, 40.41)	0.225
WHITE	4.23	(2.32, 7.69)	0
Region			
ASIA & OTHERS	3.4	(1.53, 7.52)	0
EASTERN EUROPE	5.03	(2.01, 12.62)	0
NORTH AMERICA	7.94	(1.04, 60.71)	0.102
SOUTH AMERICA	4.95	(0.63, 38.64)	0.234
WESTERN EUROPE	2.86	(1.10, 7.40)	0.014

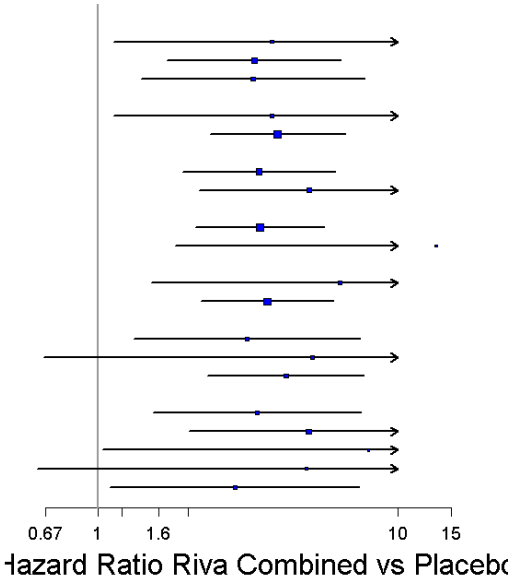
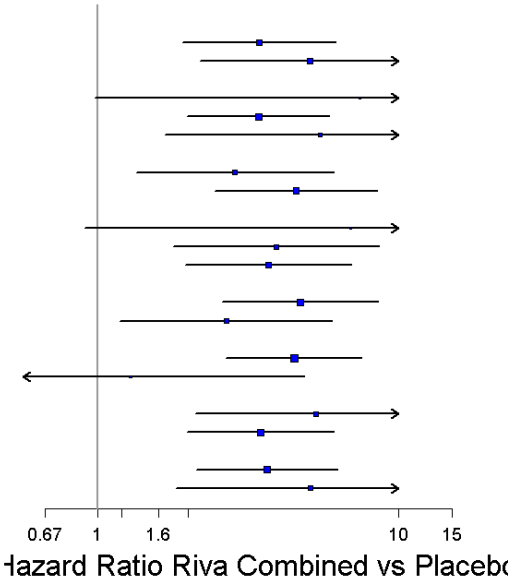


Figure 24. Effect of Combined Rivaroxaban Compared with Placebo on Non-CABG-Related TIMI Major Bleeding Events

	HR	95% CI	P-Value
By Rand Seq			
first	3.44	(1.92, 6.17)	0
second	5.08	(2.19, 11.75)	0
Weight			
< 60	7.42	(0.98, 56.43)	0.053
60-90	3.42	(1.99, 5.89)	0
>= 90	5.47	(1.68, 17.82)	0.005
BMI			
<= 25	2.86	(1.35, 6.08)	0.006
25-35	4.56	(2.45, 8.51)	0
CRCL			
30-50 mL	6.92	(0.91, 52.93)	0.062
50-80 mL	3.93	(1.79, 8.62)	0.001
>80 mL	3.69	(1.96, 6.94)	0
Prior MI			
N	4.71	(2.59, 8.54)	0
Y	2.68	(1.19, 6.00)	0.017
CHF			
N	4.49	(2.67, 7.52)	0
Y	1.29	(0.34, 4.86)	0.707
Hypertension			
N	5.32	(2.12, 13.32)	0
Y	3.47	(1.98, 6.08)	0
Diabetes			
N	3.66	(2.13, 6.28)	0
Y	5.08	(1.82, 14.19)	0.002



Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

Figure 25. Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on Non-CABG-Related TIMI Major Bleeding Events

	HR	95% CI	P-Value
By Rand Seq			
first	2.9	(1.54, 5.46)	0.001
second	4.67	(1.93, 11.28)	0.001
Weight			
< 60	7.53	(0.93, 61.23)	0.059
60-90	3.08	(1.72, 5.52)	0
>= 90	4.09	(1.17, 14.35)	0.028
BMI			
<= 25	2.74	(1.21, 6.18)	0.015
25-35	3.76	(1.94, 7.32)	0
CRCL			
30-50 mL	7.98	(1.00, 63.80)	0.05
50-80 mL	3.26	(1.40, 7.60)	0.006
>80 mL	3.16	(1.60, 6.23)	0.001
Prior MI			
N	4.21	(2.24, 7.90)	0
Y	2.17	(0.89, 5.33)	0.09
CHF			
N	4.01	(2.32, 6.94)	0
Y	0.65	(0.11, 3.88)	0.634
Hypertension			
N	4	(1.50, 10.66)	0.006
Y	3.26	(1.79, 5.94)	0
Diabetes			
N	3	(1.67, 5.39)	0
Y	5.16	(1.77, 15.03)	0.003

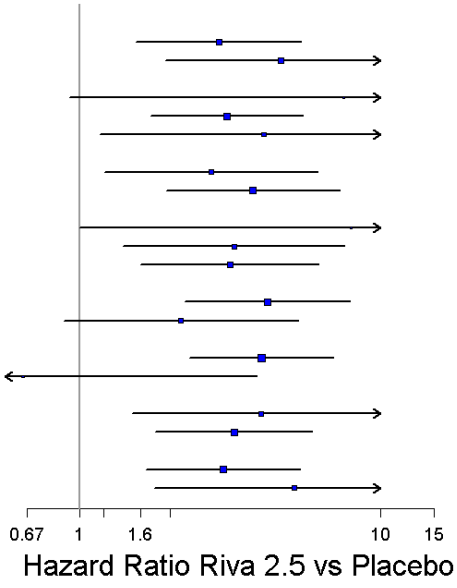
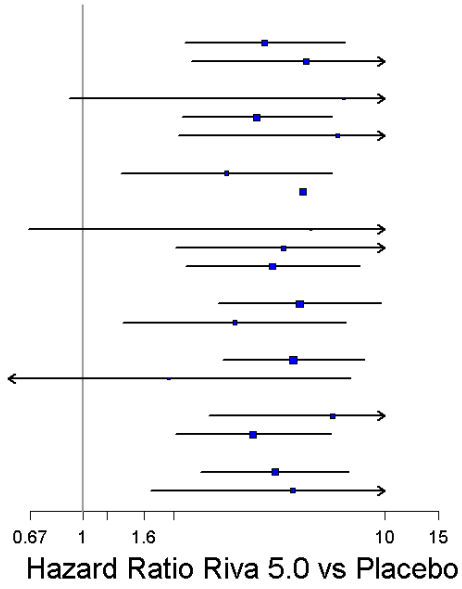


Figure 26. Effect of Rivaroxaban 5 mg BID Compared with Placebo on Non-CABG-Related TIMI Major Bleeding Events

	HR	95% CI	P-Value
By Rand Seq			
first	4	(2.17, 7.36)	0
second	5.47	(2.29, 13.09)	0
Weight			
< 60	7.29	(0.90, 59.25)	0.063
60-90	3.76	(2.13, 6.66)	0
>= 90	6.96	(2.07, 23.43)	0.002
BMI			
<= 25	2.99	(1.34, 6.68)	0.008
25-35	5.36	(2.81, 10.22)	0
CRCL			
30-50 mL	5.67	(0.66, 48.56)	0.113
50-80 mL	4.6	(2.03, 10.39)	0
>80 mL	4.24	(2.19, 8.22)	0
Prior MI			
N	5.22	(2.81, 9.71)	0
Y	3.18	(1.36, 7.44)	0.008
CHF			
N	4.97	(2.90, 8.53)	0
Y	1.92	(0.48, 7.67)	0.357
Hypertension			
N	6.7	(2.61, 17.20)	0
Y	3.66	(2.03, 6.63)	0
Diabetes			
N	4.32	(2.46, 7.58)	0
Y	4.95	(1.68, 14.55)	0.004



Source: Steve Bai, Ph.D., Division of Biometrics I, FDA

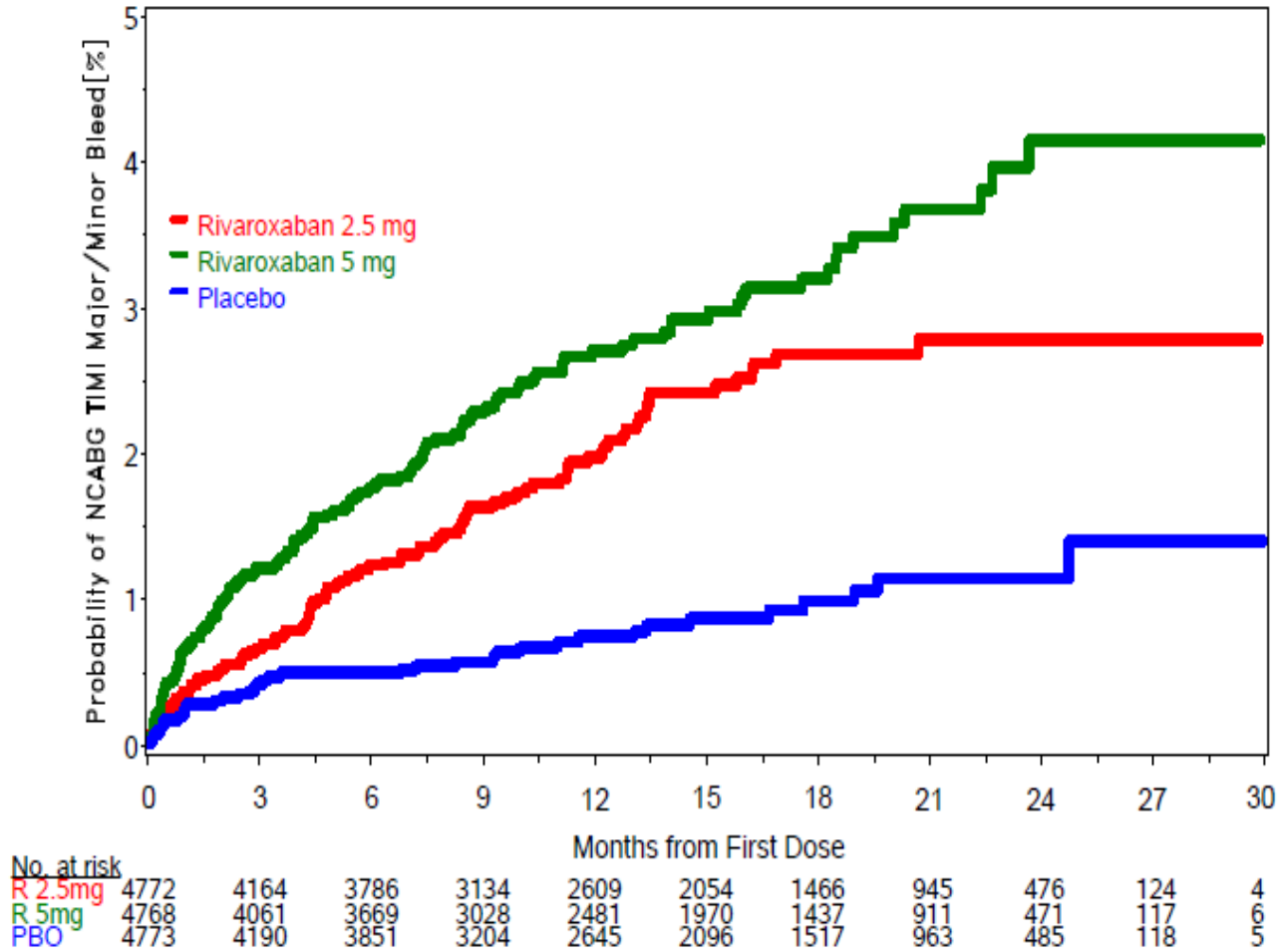
7.3.4.2 Other Bleeding Events

Please see Table 36, Table 37, and Table 38 for the following TIMI bleeding rates:

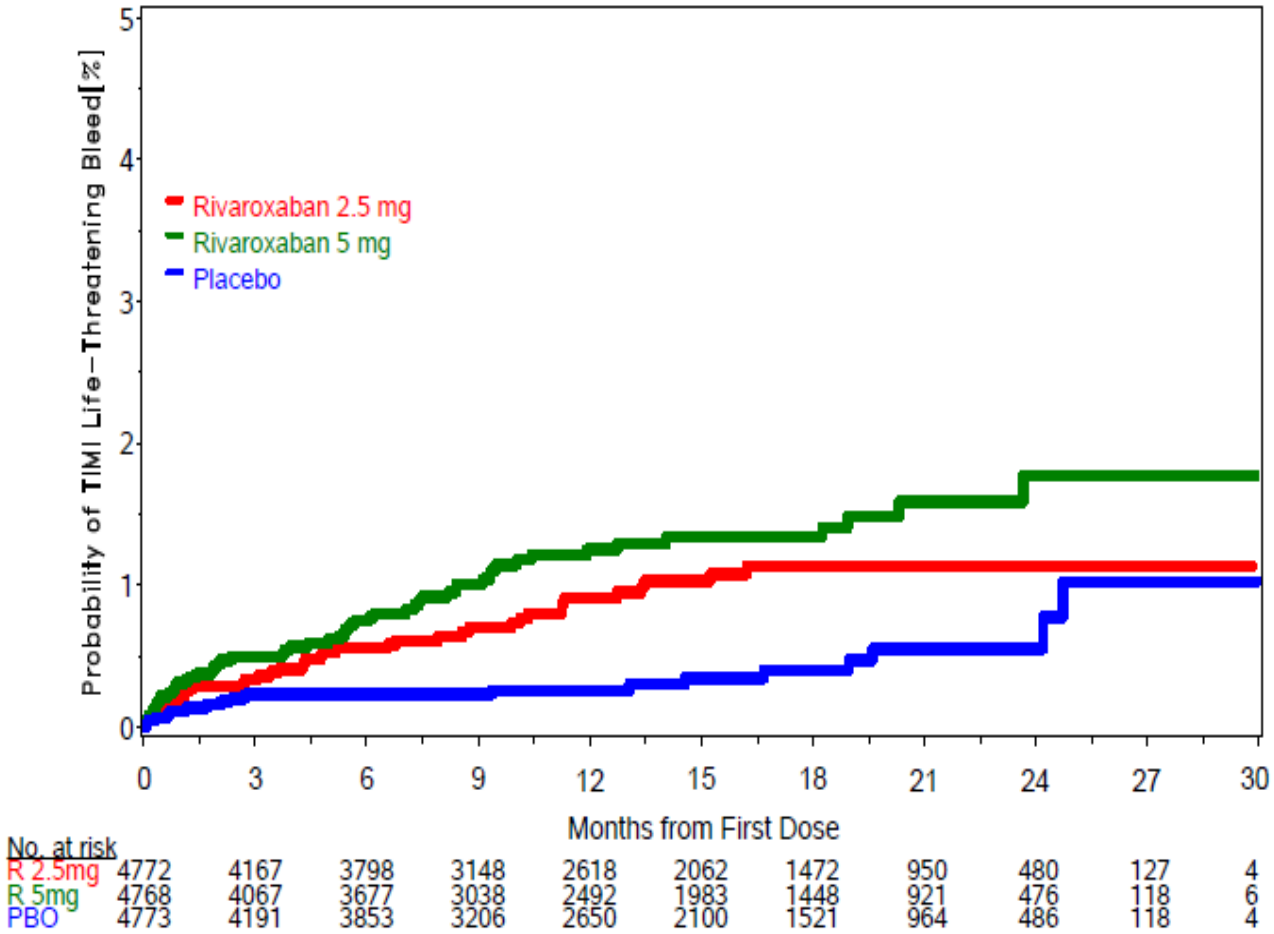
- All Bleeding (CABG + Non-CABG-Related Bleeding)
- CABG-Related Bleeding
- Non-CABG-Related Bleeding

A summary of the findings is included in the Safety Summary at the beginning of Section 7.

7.3.4.2.1 Time to Non-CABG-Related TIMI Major/Minor Bleeding Event (Stratum 2)



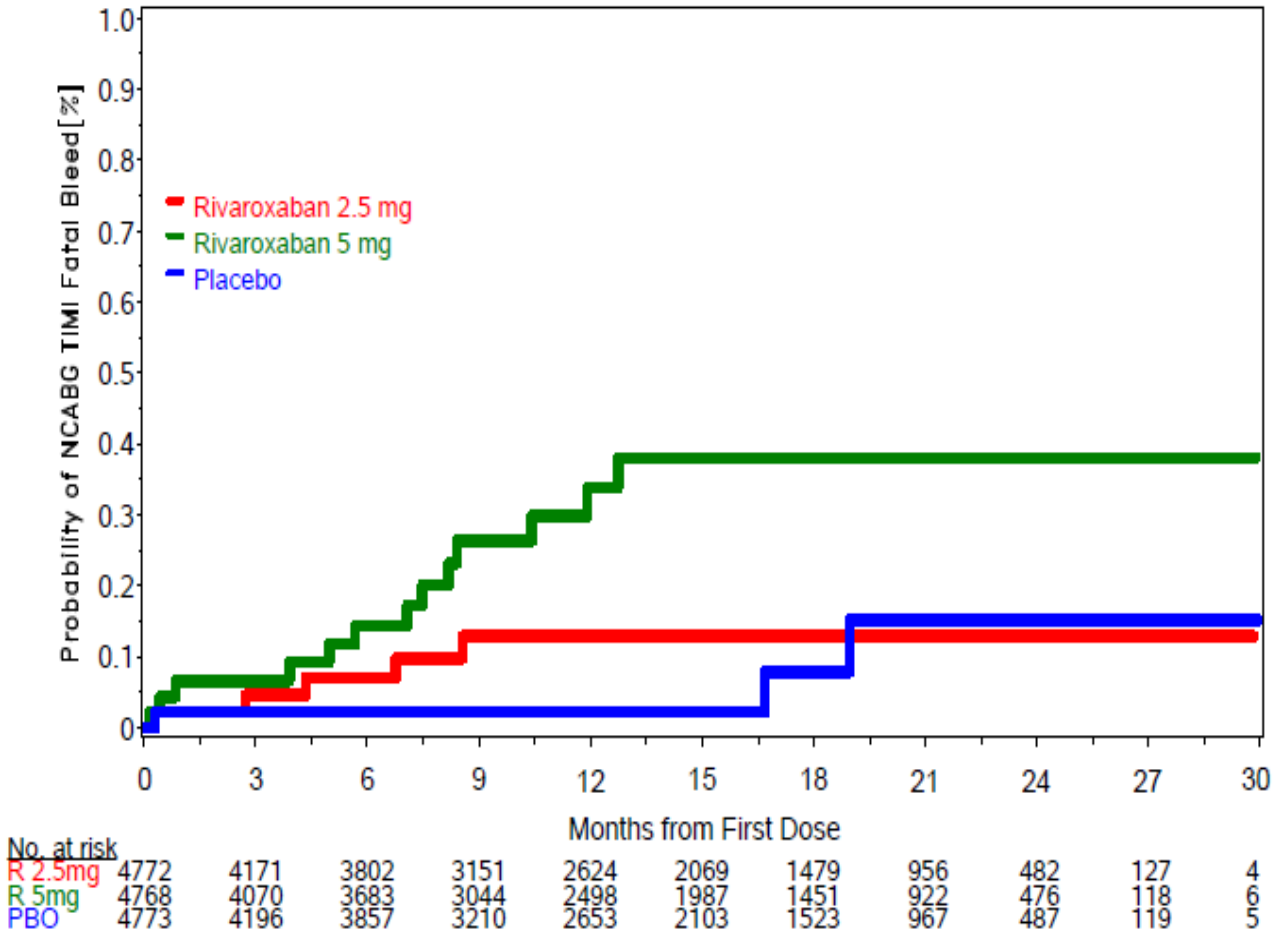
7.3.4.2.2 Time to Non-CABG TIMI Life-Threatening Bleeding Event (Stratum 2)



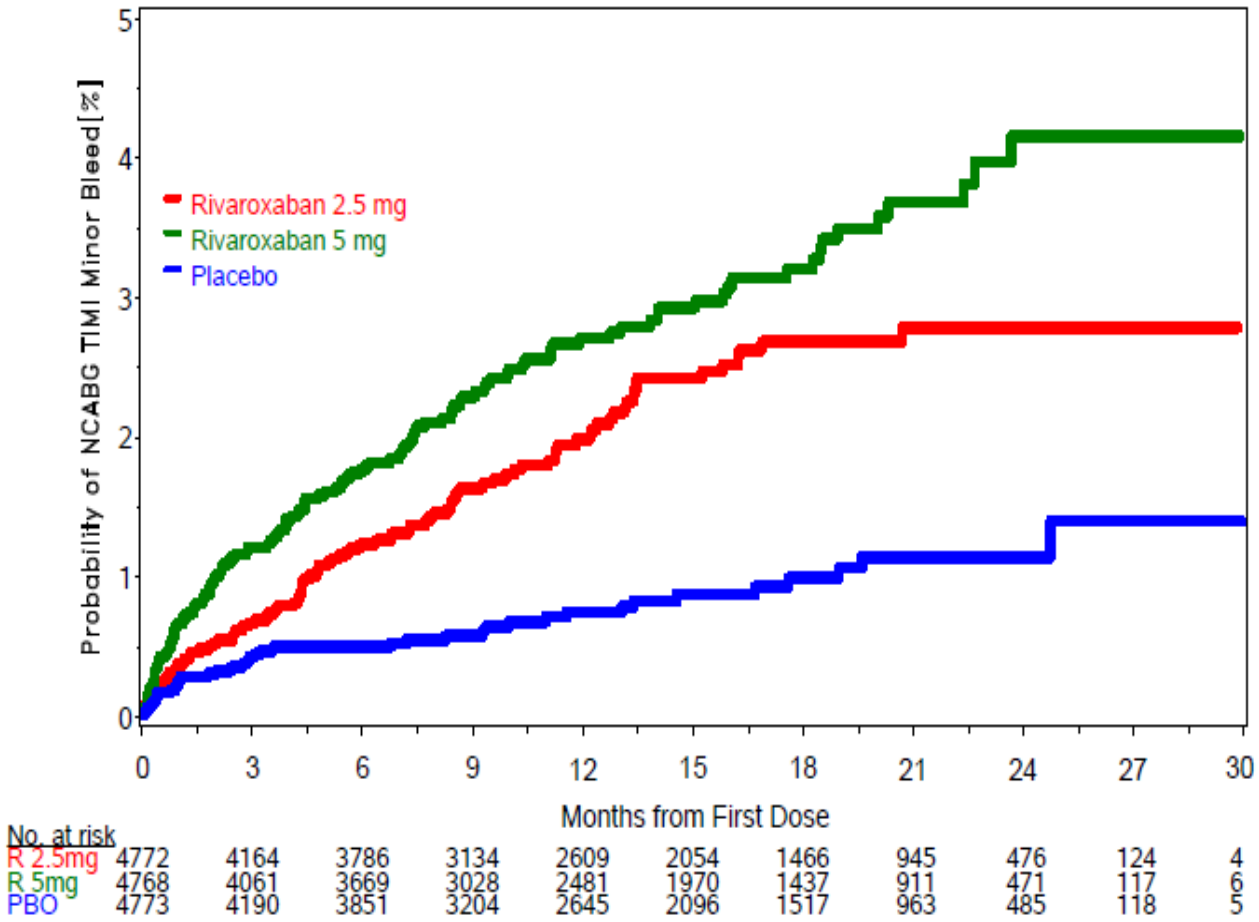
No. at risk

R 2.5mg	4772	4167	3798	3148	2618	2062	1472	950	480	127	4
R 5mg	4768	4067	3677	3038	2492	1983	1448	921	476	118	6
PBO	4773	4191	3853	3206	2650	2100	1521	964	486	118	4

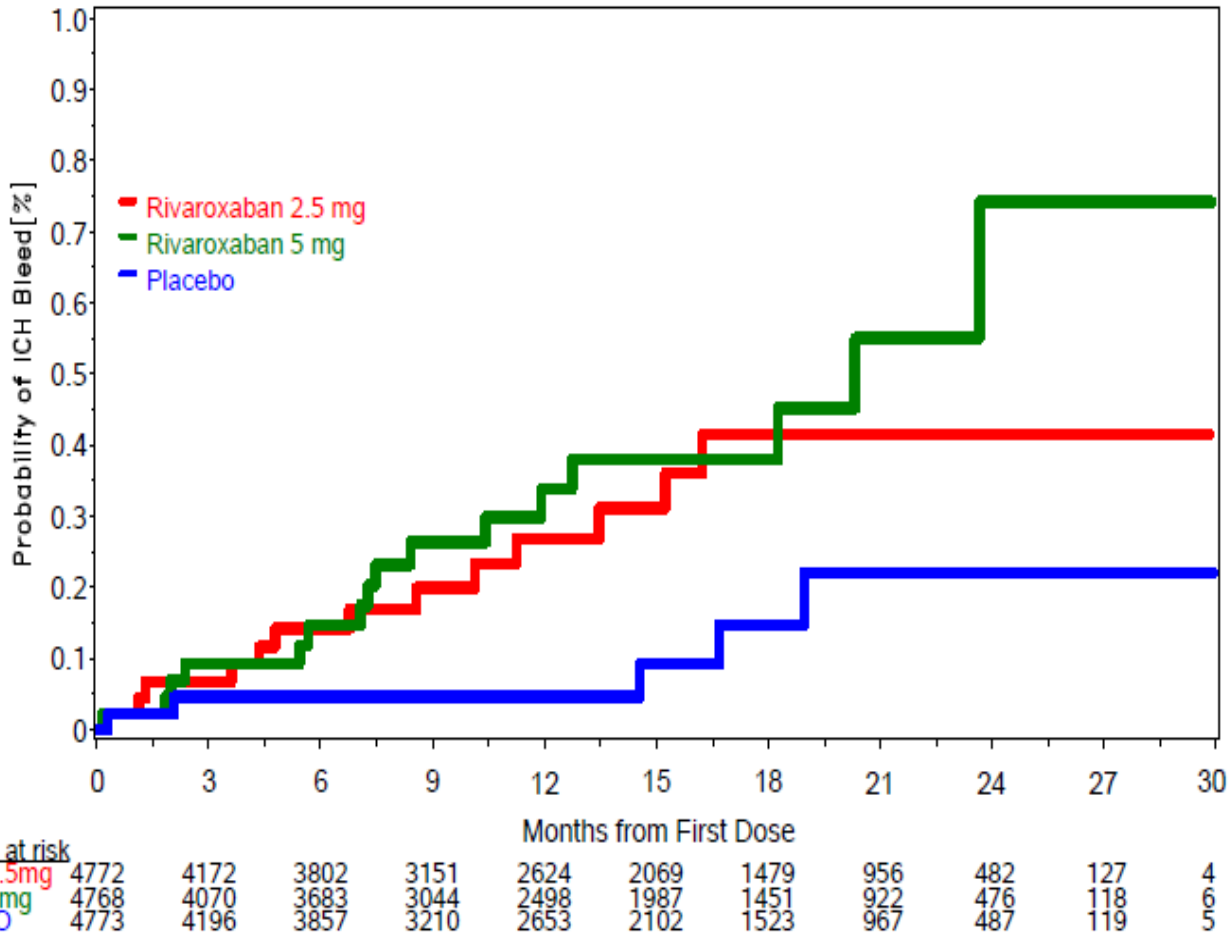
7.3.4.2.3 Time to Non-CABG-Related TIMI Major Fatal Bleeding Event (Stratum 2)



7.3.4.2.4 Time to Non-CABG-Related TIMI Minor Bleeding Event (Stratum 2)



7.3.4.2.5 Time to Non-CABG-Related Intracranial Hemorrhage (Stratum 2)



No. at risk

R 2.5mg	4772	4172	3802	3151	2624	2069	1479	956	482	127	4
R 5mg	4768	4070	3683	3044	2498	1987	1451	922	476	118	6
PBO	4773	4196	3857	3210	2653	2102	1523	967	487	119	5

Table 36. Effect of Rivaroxaban Compared to Placebo on All Bleeding (Treatment Emergent + 2 Days)

Subject Stratum Parameter	Rivaroxaban						Placebo		2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID		5 mg BID		Combined									
	(N = 5115) n (%)	Event Rate (100 pt-yr)	(N = 5110) n (%)	Event Rate (100 pt-yr)	(N = 10225) n (%)	Event Rate (100 pt-yr)	(N = 5125) n (%)	Event Rate (100 pt-yr)	HR	(95% CI)	HR	95% CI	HR	95% CI
ALL STRATA	**5115**		**5110**		**10225**		**5125**							
TIMI Major or Minor Bleeding	100 (2.0)	1.80	132 (2.6)	2.45	232 (2.3)	2.12	46 (0.9)	0.82	2.20	(1.55, 3.11)	2.96	(2.12, 4.14)	2.58	(1.88, 3.54)
TIMI Major Bleeding	68 (1.3)	1.22	85 (1.7)	1.57	153 (1.5)	1.40	27 (0.5)	0.48	2.55	(1.63, 3.98)	3.25	(2.11, 5.02)	2.90	(1.92, 4.36)
TIMI Major Fatal	6 (0.1)	0.11	13 (0.3)	0.24	19 (0.2)	0.17	5 (< 0.1)	0.09	1.21	(0.37, 3.98)	2.70	(0.96, 7.56)	1.94	(0.73, 5.20)
TIMI Life-Threatening Bleeding	41 (0.8)	0.74	57 (1.1)	1.05	98 (1.0)	0.89	19 (0.4)	0.34	2.18	(1.26, 3.75)	3.09	(1.84, 5.20)	2.63	(1.61, 4.30)
ICH	14 (0.3)	0.25	18 (0.4)	0.33	32 (0.3)	0.29	5 (<0.1)	0.09	2.83	(1.02, 7.86)	3.74	(1.39, 10.1)	3.28	(1.28, 8.42)
ICH Fatal	5 (<0.1)	0.09	8 (0.2)	0.15	13 (0.1)	0.12	4 (<0.1)	0.07	1.27	(0.34, 4.72)	2.09	(0.63, 6.93)	1.67	(0.54, 5.11)
TIMI Minor Bleeding	32 (0.6)	0.58	49 (1.0)	0.91	81 (0.8)	0.74	20 (0.4)	0.36	1.62	(0.92, 2.82)	2.52	(1.50, 4.24)	2.07	(1.27, 3.37)
Clinically Significant Bleeding	586 (11.5)	11.17	748 (14.6)	14.94	1334 (13.0)	13.01	327 (6.4)	6.01	1.84	(1.61, 2.11)	2.43	(2.13, 2.76)	2.13	(1.89, 2.40)
TIMI Medical Attention	492 (9.6)	9.33	637 (12.5)	12.66	1129 (11.0)	10.96	282 (5.5)	5.17	1.79	(1.55, 2.07)	2.39	(2.08, 2.75)	2.09	(1.83, 2.38)

Subject Stratum Parameter	Rivaroxaban						Placebo		2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID		5 mg BID		Combined									
	(N = 5115) n (%)	Event Rate (100 pt-yr)	(N = 5110) n (%)	Event Rate (100 pt-yr)	(N = 10225) n (%)	Event Rate (100 pt-yr)	(N = 5125) n (%)	Event Rate (100 pt-yr)	HR	(95% CI)	HR	95% CI	HR	95% CI
STRATUM 1	**343**		**342**		**685**		**352**							
TIMI Major or Minor Bleeding	3 (0.9)	0.84	4 (1.2)	1.11	7 (1.0)	0.98	2 (0.6)	0.56	1.53	(0.26, 9.16)	2.00	(0.37, 10.9)	1.77	(0.37, 8.50)
TIMI Major Bleeding	2 (0.6)	0.56	4 (1.2)	1.11	6 (0.9)	0.84	2 (0.6)	0.56	1.02	(0.14, 7.22)	2.00	(0.37, 10.9)	1.51 (0.30), 7.47)	(0.30), 7.47)
TIMI Major Fatal	1 (0.3)	0.28	0		1 (0.1)	0.14	1 (0.3)	0.28	1.01	(0.06, 16.1)			0.50	(0.03, 8.00)
TIMI Life-Threatening Bleeding	1 (0.3)	0.28	3 (0.9)	0.83	4 (0.6)	0.56	1 (0.3)	0.28	1.01	(0.06, 16.1)	2.97	(0.31, 28.6)	2.00	(0.22, 17.9)
ICH	1 (0.3)	0.28	2 (0.6)	0.55	3 (0.4)	0.42	0							
ICH Fatal	1 (0.3)	0.28	0		1 (0.1)	0.14	0							
TIMI Minor Bleeding	1 (0.3)	0.28	0		1 (0.1)	0.14	0							
Clinically Significant Bleeding	19 (5.5)	5.46	23 (6.7)	6.53	42 (6.1)	6.00	11 (3.1)	3.11	1.77	(0.84, 3.71)	2.10	(1.02, 4.31)	1.93	(0.99, 3.75)
TIMI Medical Attention	16 (4.7)	4.60	19 (5.6)	5.40	35 (5.1)	5.00	9 (2.6)	2.54	1.82	(0.81, 4.13)	2.13	(0.96, 4.70)	1.97	(0.95, 4.10)

Subject Stratum Parameter	Rivaroxaban						Placebo		2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID		5 mg BID		Combined									
	(N = 5115) n (%)	Event Rate (100 pt-yr)	(N = 5110) n (%)	Event Rate (100 pt-yr)	(N = 10225) n (%)	Event Rate (100 pt-yr)	(N = 5125) n (%)	Event Rate (100 pt-yr)	HR	(95% CI)	HR	95% CI	HR	95% CI
STRATUM 2	**4772**		**4768**		**9540**		**4773**							
TIMI Major or Minor Bleeding	97 (2.0)	1.87	128 (2.7)	2.54	225 (2.4)	2.20	44 (0.9)	0.84	2.23	(1.56, 3.18)	3.01	(2.13, 4.23)	2.62	(1.89, 3.61)
TIMI Major Bleeding	66 (1.4)	1.27	81 (1.7)	1.61	147 (1.5)	1.44	25 (0.5)	0.47	2.67	(1.68, 4.23)	3.35	(2.14, 5.25)	3.01	(1.97, 4.60)
TIMI Major Fatal	5 (0.1)	0.10	13 (0.3)	0.26	18 (0.2)	0.18	4 (< 0.1)	0.08	1.27	(0.34, 4.72)	3.38	(1.10, 10.4)	2.30	(0.78, 6.81)
TIMI Life-Threatening Bleeding	40 (0.8)	0.77	54 (1.1)	1.07	94 (1.0)	0.92	18 (0.4)	0.34	2.24	(1.29, 3.91)	3.10	(1.82, 5.28)	2.67	(1.61, 4.42)
ICH	13 (0.3)	0.25	16 (0.3)	0.32	29 (0.3)	0.28	5 (0.1)	0.09	2.63	(0.94, 7.38)	3.34	(1.22, 9.12)	2.98	(1.15, 7.70)
ICH Fatal	4(<0.1)	0.08	8 (0.2)	0.16	12 (0.1)	0.12	4 (<0.1)	0.08	1.01	(0.25, 4.06)	2.09	(0.63, 6.93)	1.54	(0.50, 4.78)
TIMI Minor Bleeding	31 (0.6)	0.60	49 (1.0)	0.97	80 (0.8)	0.78	20 (0.4)	0.38	1.56	(0.89, 2.74)	2.52	(1.50, 4.24)	2.04	(1.25, 3.33)
Clinically Significant Bleeding	567 (11.9)	11.58	725 (15.2)	15.57	1292 (13.5)	13.53	316 (6.6)	6.21	1.84	(1.61, 2.12)	2.44	(2.14, 2.78)	2.14	(1.89, 2.42)
TIMI Medical Attention	476 (10.0)	9.67	618 (13.0)	13.20	1094 (11.5)	11.39	273 (5.7)	5.35	1.79	(1.54, 2.07)	2.40	(2.08, 2.77)	2.09	(1.83, 2.39)
Analysis verified by Karen A. Hicks, M.D.														

Table 37. Effect of Rivaroxaban Compared to Placebo on CABG-Related Bleeding Events (Treatment Emergent + Days)

Subject Stratum Parameter	Rivaroxaban						Placebo		2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID		5 mg BID		Combined									
	(N = 111 n (%)	Event Rate (100 pt-yr)	(N = 97) n (%)	Event Rate (100 pt-yr)	(N = 208) n (%)	Event Rate (100 pt-yr)	(N = 108) n (%)	Event Rate (100 pt-yr)	HR	(95% CI)	HR	95% CI	HR	95% CI
ALL STRATA	**111**		**97**		**208**		**108**							
TIMI Major or Minor Bleeding	3 (2.7)	2.17	3 (3.1)	2.53	6 (2.9)	2.34	8 (7.4)	6.71	0.37	(0.10, 1.39)	0.41	(0.11, 1.55)	0.38	(0.13, 1.11)
TIMI Major Bleeding	3 (2.7)	2.17	3(3.1)	2.53	6 (2.9)	2.34	8 (7.4)	6.71	0.37	(0.10, 1.39)	0.41	(0.11, 1.55)	0.38	(0.13, 1.11)
TIMI Major Fatal	0		0		0		2 (1.9)	1.58						
STRATUM 1	**7**		**11**		**18**		**12**							
TIMI Major or Minor Bleeding	0		0		0		2 (16.7)	29.35						
TIMI Major Bleeding	0		0		0		2 (16.7)	29.35						
TIMI Major Fatal	0		0		0		1 (8.3)	13.16						
STRATUM 2	**104**		**86**		**190**		**96**							
TIMI Major or Minor Bleeding	3 (2.9)	2.30	3 (3.5)	2.87	6 (3.2)	2.55	6 (6.3)	5.33	0.45	(0.11, 1.79)	0.56	(0.14, 2.23)	0.50	(0.16, 1.54)
TIMI Major Bleeding	3 (2.9)	2.30	3 (3.5)	2.87	6 (3.2)	2.55	6 (6.3)	5.33	0.45	(0.11, 1.79)	0.56	(0.14, 2.23)	0.50	(0.16, 1.54)
TIMI Major Fatal	0		0		0		1 (1.0)	0.84						

Table 38. Effect of Rivaroxaban Compared to Placebo on Non-CABG-Related Bleeding Events (Treatment Emergent + 2 Days)

Subject Stratum Parameter	Rivaroxaban						Placebo		2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID		5 mg BID		Combined									
	(N = 5115) n (%)	Event Rate (100 pt-yr)	(N = 5110) n (%)	Event Rate (100 pt-yr)	(N = 10225) n (%)	Event Rate (100 pt-yr)	(N = 5125) n (%)	Event Rate (100 pt-yr)	HR	(95% CI)	HR	95% CI	HR	95% CI
ALL STRATA	**5115**		**5110**		**10225**		**5125**							
TIMI Major or Minor Bleeding	97 (1.9)	1.75	129 (2.5)	2.39	226 (2.2)	2.07	38 (0.7)	0.68	2.58	(1.77, 3.76)	3.51	(2.44, 5.04)	3.04	(2.16, 4.29)
TIMI Major Bleeding	65 (1.3)	1.17	82 (1.6)	1.52	147 (1.4)	1.34	19 (0.4)	0.34	3.46	(2.08, 5.77)	4.47	(2.71, 7.36)	3.96	(2.46, 6.38)
TIMI Major Fatal	6 (0.1)	0.11	13 (0.3)	0.24	19 (0.2)	0.17	3 (< 0.1)	0.05	2.03	(0.51, 8.10)	4.51	(1.28, 15.8)	3.24	(0.96, 11.0)
TIMI Life-Threatening Bleeding	37 (0.7)	0.67	54 (1.1)	1.00	91 (0.9)	0.83	13 (0.3)	0.23	2.87	(1.53, 5.41)	4.29	(2.34, 7.86)	3.57	(2.00, 6.39)
ICH	14 (0.3)	0.25	18 (0.4)	0.33	32 (0.3)	0.29	4 (< 0.1)	0.07	3.54	(1.17, 10.8)	4.68	(1.58, 13.8)	4.10	(1.45, 11.6)
ICH Fatal	5 (<0.1)	0.09	8 (0.2)	0.15	13 (0.1)	0.12	3(<0.1)	0.05	1.69	(0.40, 7.07)	2.79	(0.74, 10.5)	2.22	(0.63, 7.81)
TIMI Minor Bleeding	32 (0.6)	0.58	49 (1.0)	0.91	81 (0.8)	0.74	20 (0.4)	0.36	1.62	(0.92, 2.82)	2.52	(1.50, 4.24)	2.07	(1.27, 3.37)
Clinically Significant Bleeding	584 (11.4)	11.13	745 (14.6)	14.87	1329 (13.0)	12.96	318 (6.2)	5.83	1.89	(1.65, 2.16)	2.49	(2.18, 2.84)	2.18	(1.93, 2.47)
TIMI Medical Attention	492 (9.6)	9.33	637 (12.5)	12.66	1129 (11.0)	10.96	280 (5.5)	5.13	1.80	(1.56, 2.09)	2.41	(2.09, 2.77)	2.10	(1.84, 2.39)

Subject Stratum Parameter	Rivaroxaban						Placebo		2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID		5 mg BID		Combined									
	(N = 5115) n (%)	Event Rate (100 pt-yr)	(N = 5110) n (%)	Event Rate (100 pt-yr)	(N = 10225) n (%)	Event Rate (100 pt-yr)	(N = 5125) n (%)	Event Rate (100 pt-yr)	HR	(95% CI)	HR	95% CI	HR	95% CI
STRATUM 1	**343**		**342**		**685**		**352**							
TIMI Major or Minor Bleeding	3 (0.9)	0.84	4 (1.2)	1.11	7 (1.0)	0.98	0							
TIMI Major Bleeding	2 (0.6)	0.56	4 (1.2)	1.11	6 (0.9)	0.84	0							
TIMI Major Fatal	1 (0.3)	0.28	0		1 (0.1)	0.14	0							
TIMI Life-Threatening Bleeding	1 (0.3)	0.28	3 (0.9)(0.9)0.83	0.83	4 (0.6)	0.56	0							
ICH	1 (0.3)	0.28	2 (0.6)	0.55	3 (0.4)	0.42	0							
ICH Fatal	1 (0.3)	0.28	0		1 (0.1)	0.14	0							
TIMI Minor Bleeding	1 (0.3)	0.28	0		1 (0.1)	0.14	0							
Clinically Significant Bleeding	19 (5.5)	5.46	23 (6.7)	6.53	42 (6.1)	6.00	9 (2.6)	2.54	2.16	(0.98, 4.78)	2.57	(1.19, 5.56)	2.37	(1.15, 4.86)
TIMI Medical Attention	16 (4.7)	4.60	19 (5.6)	5.40	35 (5.1)	5.00	9 (2.6)	2.54	1.82	(0.81, 4.13)	2.13	(0.96, 4.70)	1.97	(0.95, 4.10)

Subject Stratum Parameter	Rivaroxaban						Placebo		2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID		5 mg BID		Combined									
	(N = 5115) n (%)	Event Rate (100 pt-yr)	(N = 5110) n (%)	Event Rate (100 pt-yr)	(N = 10225) n (%)	Event Rate (100 pt-yr)	(N = 5125) n (%)	Event Rate (100 pt-yr)	HR	(95% CI)	HR	95% CI	HR	95% CI
STRATUM 2	**4772**		**4768**		**9540**		**4773**							
TIMI Major or Minor Bleeding	94 (2.0)	1.81	125 (2.6)	2.48	219 (2.3)	2.14	38 (0.8)	0.72	2.50	(1.72, 3.65)	3.40	(2.37, 4.89)	2.95	(2.09, 4.16)
TIMI Major Bleeding	63 (1.3)	1.21	78 (1.6)	1.55	141 (1.5)	1.38	19 (0.4)	0.36	3.35	(2.01, 5.60)	4.26	(2.58, 7.03)	3.80	(2.35, 6.14)
TIMI Major Fatal	5 (0.1)	0.10	13 (0.3)	0.26	18 (0.2)	0.18	3 (<0.1)	0.06	1.69	(0.40, 7.07)	4.51	(1.28, 15.8)	3.07	(0.91, 10.4)
TIMI Life-Threatening Bleeding	36 (0.8)	0.69	51 (1.1)	1.01	87 (0.9)	0.85	13 (0.3)	0.25	2.80	(1.48, 5.27)	4.06	(2.21, 7.46)	3.42	(1.91, 6.13)
ICH	13 (0.3)	0.25	16 (0.3)	0.32	29 (0.3)	0.28	4 (<0.1)	0.08	3.29	(1.07, 10.1)	4.18	(1.40, 12.5)	3.73	(1.31, 10.6)
ICH Fatal	4 (<0.1)	0.08	8 (0.2)	0.16	12 (0.1)	0.12	3 (<0.1)	0.06	1.35	(0.30, 6.05)	2.79	(0.74, 10.5)	2.06	(0.58, 7.29)
TIMI Minor Bleeding	31 (0.6)	0.60	49 (1.0)	0.97	80 (0.8)	0.78	20 (0.4)	0.38	1.56	(0.89, 2.74)	2.52	(1.50, 4.24)	2.04	(1.25, 3.33)
Clinically Significant Bleeding	565 (11.8)	11.54	722 (15.1)	15.50	1287 (13.5)	13.47	309 (6.5)	6.06	1.88	(1.64, 2.16)	2.48	(2.17, 2.84)	2.18	(1.92, 2.47)
TIMI Medical Attention	476 (10.0)	9.67	618 (13.0)	13.20	1094 (11.5)	11.39	271 (5.7)	5.30	1.80	(1.55, 2.09)	2.42	(2.10, 2.79)	2.11	(1.84, 2.40)
Analysis verified by Karen A. Hicks, M.D.														

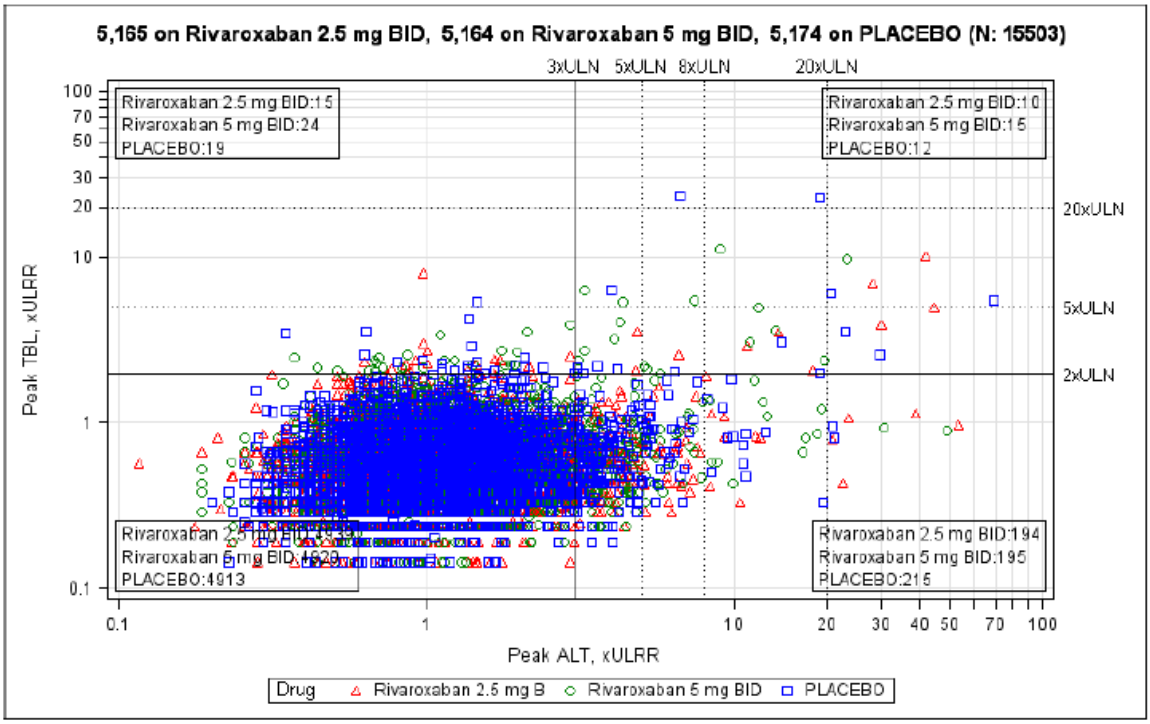
7.3.4.4 Fatal Life-Threatening Bleeding Events

In the treatment emergent + 2 day analysis set, there were 6, 15, and 9 fatal life-threatening hemorrhages on rivaroxaban 2.5 mg BID, rivaroxaban 5 mg BID, and placebo, respectively, as shown in Table 39. Most of these fatal hemorrhages were due to intracranial or gastrointestinal bleeding. Fatal intracranial bleeding occurred in 4, 5, and 8 subjects on placebo, rivaroxaban 2.5 mg BID, and rivaroxaban 5 mg BID. One subject on rivaroxaban 2.5 mg BID and six subjects on rivaroxaban 5 mg BID had fatal gastrointestinal bleeding events.

7.3.5 Submission Specific Primary Safety Concerns

Dr. Senior from the Office of Pharmacovigilance and Epidemiology was consulted to evaluate 37 cases of elevated serum alanine aminotransferase (ALT) and total bilirubin (TBL) from TIMI 51 that were in the right-upper quadrant (northeast quadrant), as shown in Figure 27. Dr. Senior also reviewed 6 cases of ALT and TBL elevation in the northeast quadrant from TIMI 46. His review was notable for a number of possible or probable cases of drug-induced liver injury that were severe enough to raise the serum bilirubin concentration. There were no cases of severe liver injury. Many of these

Figure 27. TIMI 51 data



Review by John Senior, M.D., Office of Pharmacovigilance and Epidemiology, 4/19/2012.

Table 39. Life-Threatening Fatal Hemorrhage (Treatment Emergent + 2 Days)

USUBJID	Treatment Group	Stratum	Age	Sex	Weight (kg)	CrCl	Ethnicity	Type
081014-305337	Placebo	2	49	M	70.3 kg	> 80	Asian	Intracranial-Subarachnoid hemorrhage
090009-303765	Placebo	2	65	M	73	≥50 - ≤80	Caucasian	Intracranial—intraparenchymal/subdural
381006-306321	Placebo	2	57	M	73.5	> 80	Caucasian	Intracranial--intraparenchymal
380028-310263	Placebo	2	59	F	59	> 80	Caucasian	Intracranial—intraparenchymal/subarachnoid
055026-315013	Placebo	1	82	M	63.4	≥50 - ≤80	Caucasian	Internal bleeding (non-incisional site) associated
007022-300300	Placebo	2	69	F	70.2	≥50 - ≤80	Caucasian	Pericardial
048040-301649	Placebo	2	72	M	72	≥50 - ≤80	Caucasian	TIMI Major - Other
380018-314727	Placebo	2	71	F	83	≥ 30 – < 50	Caucasian	Pericardial
380024-310724	Placebo	2	62	M	98	> 80	Caucasian	Pericardial
086027-314913	Rivaroxaban 2.5 mg BID	2	52	M	75	> 80	Asian	Intracranial--intraparenchymal
091022-301927	Rivaroxaban 2.5 mg BID	1	77	M	82	≥50 - ≤80	Asian	Intracranial--intraparenchymal
091031-305079	Rivaroxaban 2.5 mg BID	2	56	M	55	≥ 30 – < 50	Asian	Intracranial--intraparenchymal
091077-310520	Rivaroxaban 2.5 mg BID	2	70	M	62	≥ 30 – < 50	Asian	Intracranial—intraparenchymal/intraventricular
380018-309092	Rivaroxaban 2.5 mg BID	2	53	M	72	≥50 - ≤80	Caucasian	Intracranial—intraparenchymal/intraventricular

USUBJID	Treatment Group	Stratum	Age	Sex	Weight (kg)	CrCl	Ethnicity	Type
007004-304173	Rivaroxaban 2.5 mg BID	2	74	M	77	≥ 30 – < 50	Caucasian	GI (Hematemesis or Melena)
007020-306771	Rivaroxaban 5 mg BID	2	61	M	102	> 80	Caucasian	Intracranial—intraparenchymal/ intraventricular
060001-314524	Rivaroxaban 5 mg BID	2	56	M	74	> 80	Asian	Intracranial—intraventricular/ subarachnoid
066005-305288	Rivaroxaban 5 mg BID	2	56	M	68	≥50 - ≤80	Asian	Intracranial--subarachnoid
086029-310433	Rivaroxaban 5 mg BID	2	71	F	79.5	> 80	Asian	Intracranial--intraparenchymal
091006-302924	Rivaroxaban 5 mg BID	2	70	M	64.9	≥ 30 – < 50	Asian	Intracranial--intraparenchymal
091008-305074	Rivaroxaban 5 mg BID	2	58	M	78.2	> 80	Asian	Intracranial--intraventricular
420003-301821	Rivaroxaban 5 mg BID	2	60	M	124	> 80	Caucasian	Intracranial/ intraparenchymal/ intraventricular/ subarachnoid
007012-304127	Rivaroxaban 5 mg BID	2	65	M	82.4	> 80	Caucasian	TIMI Major—gastrointestinal (hematemesis or melena)
036005-306402	Rivaroxaban 5 mg BID	2	86	F	61	>=30 and < 50	Caucasian	Gastrointestinal (hematemesis or melena)
216006-311523	Rivaroxaban 5 mg BID	2	59	M	81	> 80	Caucasian	Gastrointestinal (hematemesis or melena)
351003-305936	Rivaroxaban 5 mg BID	2	65	M	79	>=50 and <= 80	Caucasian	TIMI Major—Gastrointestinal (hematemesis or melena)

USUBJID	Treatment Group	Stratum	Age	Sex	Weight (kg)	CrCl	Ethnicity	Type
420002-310934	Rivaroxaban 5 mg BID	2	57	M	80	> 80	Hispanic/ Caucasian	TIMI Major—Gastrointestinal (hematemesis or melena)
054030-305853	Rivaroxaban 5 mg BID	2	77	F	62	>=30 and < 50 mL/min.	Caucasian	TIMI Major—Gastrointestinal (hematemesis or melena)
007042-301350	Rivaroxaban 5 mg BID	2	60	M	75	> 80	Caucasian	Pericardial
090013-307421	Rivaroxaban 5 mg BID	2	43	M	97.2	>80	Caucasian	Intracranial/ intraventricular

In conclusion:

> "Compared to other populations (e.g., nonvalvular atrial fibrillation; prophylaxis of deep vein thrombosis), ACS subjects, who were placed on rivaroxaban immediately after the index event and frequently had serum AST, ALT, and total bilirubin elevations before being started on rivaroxaban, appeared to have a more pronounced tendency for liver injury. Therefore, rivaroxaban, even in lower doses than what is recommended for other uses, appears possibly to cause mild liver injury in some patients. This finding likely reflects some increased susceptibility to drug-induced liver injury in patients with ACS."

We plan to add some additional language to the label to describe these findings.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 5667 (55.4%) subjects on rivaroxaban combined and 2694 (52.6%) subjects on placebo reported treatment-emergent adverse events. Cardiac and gastrointestinal disorders were most common. Most gastrointestinal events were bleeding-related.

Treatment-emergent adverse events occurring in at least 1% of subjects in any treatment group by system organ class and preferred term is displayed in Table 40.

Table 40. Treatment-Emergent Adverse Events in at Least 1% of Subjects in any Treatment Group by System Organ Class and Preferred Term (Safety Analysis Set) (ATLAS)

Subject Stratum: All Strata

Body System Or Organ Class Preferred Term	Rivaroxaban 2.5 mg BID (N=5115) n (%)	Rivaroxaban 5 mg BID (N=5110) n (%)	Rivaroxaban Combined (N=10225) n (%)	Placebo (N=5125) n (%)
Total no. subjects with treatment-emergent adverse events	2769 (54.1)	2898 (56.7)	5667 (55.4)	2694 (52.6)
Cardiac Disorders	905 (17.7)	934 (18.3)	1839 (18.0)	973 (19.0)
Angina Pectoris	295 (5.8)	307 (6.0)	602 (5.9)	340 (6.6)
Angina Unstable	246 (4.8)	269 (5.3)	515 (5.0)	248 (4.8)
Acute Myocardial Infarction	94 (1.8)	91 (1.8)	185 (1.8)	114 (2.2)
Myocardial Infarction	66 (1.3)	59 (1.2)	125 (1.2)	68 (1.3)
Cardiac Failure	75 (1.5)	47 (0.9)	122 (1.2)	56 (1.1)
Atrial Fibrillation	60 (1.2)	56 (1.1)	116 (1.1)	68 (1.3)
Gastrointestinal Disorders	543 (10.6)	685 (13.4)	1228 (12.0)	478 (9.3)
Gingival Bleeding	104 (2.0)	192 (3.8)	296 (2.9)	63 (1.2)
Rectal Haemorrhage	63 (1.2)	59 (1.2)	122 (1.2)	41 (0.8)
Respiratory, Thoracic and Mediastinal Disorders	496 (9.7)	582 (11.4)	1078 (10.5)	387 (7.6)
Epistaxis	268 (5.2)	350 (6.8)	618 (6.0)	141 (2.8)
Cough	63 (1.2)	58 (1.1)	121 (1.2)	74 (1.4)
Dyspnoea	56 (1.1)	65 (1.3)	121 (1.2)	79 (1.5)
Surgical and Medical Procedures	497 (9.7)	448 (8.8)	945 (9.2)	450 (8.8)
Percutaneous Coronary Intervention	249 (4.9)	247 (4.8)	496 (4.9)	240 (4.7)
Coronary Artery Bypass	82 (1.6)	76 (1.5)	158 (1.5)	77 (1.5)
Coronary Revascularisation	61 (1.2)	47 (0.9)	108 (1.1)	46 (0.9)
General Disorders and Administration Site Conditions	374 (7.3)	410 (8.0)	784 (7.7)	389 (7.6)
Chest Pain	113 (2.2)	99 (1.9)	212 (2.1)	90 (1.8)
Non-Cardiac Chest Pain	86 (1.7)	98 (1.9)	184 (1.8)	99 (1.9)
Injury, Poisoning and Procedural Complications	290 (5.7)	356 (7.0)	646 (6.3)	225 (4.4)
Contusion	75 (1.5)	92 (1.8)	167 (1.6)	53 (1.0)
Vascular Disorders	297 (5.8)	318 (6.2)	615 (6.0)	291 (5.7)
Haematoma	103 (2.0)	125 (2.4)	228 (2.2)	79 (1.5)
Hypertension	86 (1.7)	59 (1.2)	145 (1.4)	75 (1.5)
Infections and Infestations	291 (5.7)	323 (6.3)	614 (6.0)	360 (7.0)
Nasopharyngitis	45 (0.9)	33 (0.6)	78 (0.8)	52 (1.0)
Skin and Subcutaneous Tissue Disorders	262 (5.1)	275 (5.4)	537 (5.3)	228 (4.4)
Ecchymosis	82 (1.6)	89 (1.7)	171 (1.7)	53 (1.0)

Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Note: AE coding is based on MedDRA version 14.0.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different body system categories.
Note: Treatment-emergent AE is defined as the AE occurred after the first dose and up to 2 days after the last dose of study drug.
Note: AE is sorted in descending order by percentage in Combined Rivaroxaban group.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

Subject Stratum: All Strata				
	---------- Rivaroxaban ----------			
Body System Or Organ Class Preferred Term	2.5 mg BID (N=5115) n (%)	5 mg BID (N=5110) n (%)	Combined (N=10225) n (%)	Placebo (N=5125) n (%)
Investigations	262 (5.1)	274 (5.4)	536 (5.2)	251 (4.9)
Arteriogram Coronary	59 (1.2)	72 (1.4)	131 (1.3)	73 (1.4)
Alanine Aminotransferase Increased	44 (0.9)	41 (0.8)	85 (0.8)	49 (1.0)
Nervous System Disorders	232 (4.5)	282 (5.5)	514 (5.0)	239 (4.7)
Dizziness	61 (1.2)	52 (1.0)	113 (1.1)	50 (1.0)
Renal and Urinary Disorders	139 (2.7)	169 (3.3)	308 (3.0)	97 (1.9)
Haematuria	69 (1.3)	121 (2.4)	190 (1.9)	31 (0.6)

See footnotes on the first page of the table.

Source: Clinical Study Report, Table 34, page 208.
Analysis verified by Karen A. Hicks, M.D.

7.4.2 Laboratory Findings

Elevated transaminases were frequent in this trial in all treatment groups. See Section 7.3.5..

7.4.3 Vital Signs

There were no clinically relevant differences in blood pressure or heart rate in this trial.

7.4.4 Electrocardiograms (ECGs)

With respect to electrocardiograms, there were no concerning findings in ATLAS. The sponsor had previously conducted a thorough QT study with moxifloxacin control which was negative.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted.

7.4.6 Immunogenicity

There were no immunogenicity data submitted with this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See Section 7.3.4.

7.5.2 Time Dependency for Adverse Events

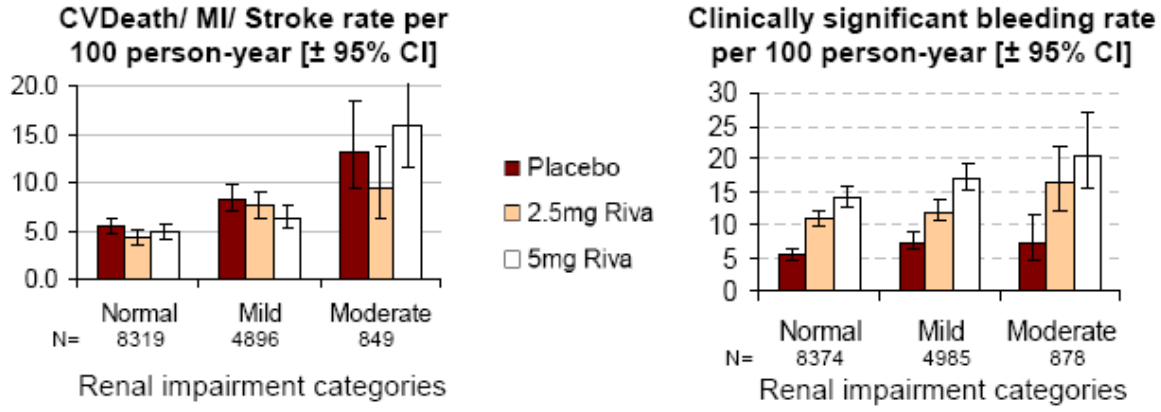
See Section 7.3.4.

7.5.3 Drug-Demographic Interactions

See Section 7.3.4.

7.5.4 Drug-Disease Interactions

In subjects with moderate renal impairment, an approximately 50% increase in total systemic exposure to rivaroxaban has been observed. In TIMI 46 and in TIMI 51, no dose adjustments were made for this population. Of the subjects enrolled in Stratum 2 of TIMI 46, only 2.6% had moderate/severe renal impairment (CrCl < 50 mL/min). About 6% of subjects enrolled in Stratum 2 had mild to moderate renal impairment (30-80 mL/min). Subjects with severe renal impairment were excluded from TIMI 51. Using TIMI 51 data, Drs. Menon-Andersen and Marathe determined that the trend for efficacy was consistent across all renal function categories while there appeared to be a trend towards increased bleeding in patients with moderate renal function, as shown in Figure 28. However, dose adjustment in this group aimed at reducing the number of bleeding events could result in loss of efficacy, therefore, no dose adjustment to less than 2.5 mg BID is recommended.



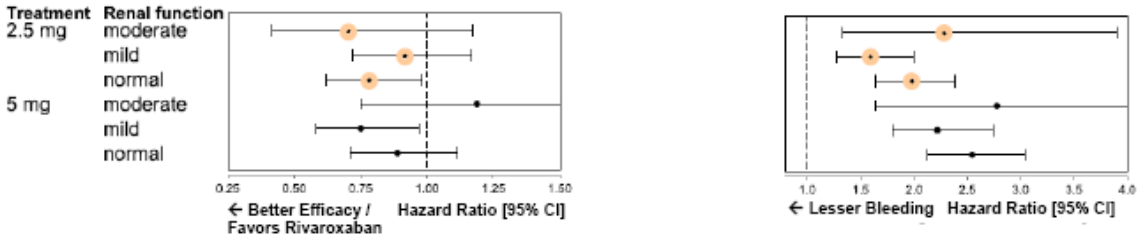


Figure 28. Efficacy and Bleeding Profile in Subjects with Moderate Renal Impairment

Efficacy and bleeding profiles in subjects with moderate renal impairment indicate that a dose adjustment in patients with moderate renal impairment is not required. Top panel: Incidence of efficacy and bleeding events by renal function category. Bottom panel: Unadjusted hazard ratios for efficacy and safety endpoints by renal function category for rivaroxaban treatment against placebo (ATLAS ACS 2 TIMI 51, Stratum 2).

Source: Review by Divya Menon-Andersen, Ph.D. and Dhananjay Marathe, Ph.D. dated 4/24/2012.

7.5.5 Drug-Drug Interactions

There were no new drug-drug interactions studies submitted with this application.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

This topic is currently under review by Dr. Marciniak.

7.6.2 Human Reproduction and Pregnancy Data

There was one pregnancy-related adverse event of post-partum hemorrhage reported in Subject 054010-306089. She was in Stratum 2 and was receiving rivaroxaban 2.5 mg daily. The dose was not changed.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessment done.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The mITT (on-treatment + 30 days) and ITT analyses we have performed to date suggest there is no rebound, but these results may be misleading if events were not well documented after study drug discontinuation. There appear to be dose-dependent increases in primary endpoint events after drug discontinuation in subjects who discontinue study drug prematurely or following the completion of the trial. Overall, however, rivaroxaban 2.5 mg BID had rates similar to placebo while rivaroxaban 5 mg BID had event rates slightly greater than placebo. Event rates on rivaroxaban were higher in the premature discontinuation group compared with the completer group.

There was one rivaroxaban "drug overdosage" reported in the adverse events dataset in Subject 216002-311356. The adverse event was deemed to be "mild" in intensity. This subject had taken 6 tablets of rivaroxaban per day from 20/07/10 to 30/08/10. He consulted the health care provider on 31/08/2010. Laboratory tests were collected and were thought to be normal. Study drug was restarted on 16/09/2010 at the same dose. This subject was in Stratum 2 on rivaroxaban 5 mg daily. The dose was not changed.

7.7 Additional Submissions / Safety Issues

One case of anaphylaxis was identified in this submission in a 65 year old woman on rivaroxaban 2.5 mg po daily (Mfr report #: RU-JNJFOC-20090504793). There are no additional safety issues at this time.

8 Postmarket Experience

A consult was placed with Ana Szarfman, M.D., Ph.D. for a review and is still pending at the time of this review. Preliminary results were remarkable for the following post-marketing signals with rivaroxaban: pulmonary embolus, hemorrhagic anemia, hepatitis, and cytolytic hepatitis.

9 Appendices

9.1 Literature Review/References

Alexander JH, Lopes RD, James S, Kilaru R, He Yaohua, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M, Huber K, Liaw D, Husted SE, Jose Lopez-Sendon, De Caterina R, Jansky P, Darius H, Vinereanu D, Cornel JH, Cools F, Atar D, Leiva-Pons JL, Keltai Matyas, Ogawa H, Pais P, Parkhomenko A, Ruzyllo W, Diaz R, White H, Ruda M, Geraldes M, Lawrence J, Harrington RA, Wallentin L for the APPRAISE-2 Investigators. Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome. N Engl J Med 2011;365:699-708.

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OASIS Investigators. Effects of Long-Term, Moderate-Intensity Oral Anticoagulation in Addition to Aspirin in Unstable Angina. J Am Coll Cardiol 2001; 37:475-84.

9.2 Labeling Recommendations

Labeling revisions are in process.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting is scheduled for Wednesday, May 23, 2012. Issues to be discussed include

- Missing data, incomplete follow-up, predominantly attributed to withdrawal of consent, and unknown vital status in over 1000 subjects at the end of the trial
- The Statistical Analysis Plan, use of a modified-Intent-to-Treat (on-treatment plus 30 days) analysis population, and late exclusion of sites 091001, 091019, and 091026
- Inconsistent efficacy results, with rivaroxaban 2.5 mg BID primarily reducing CV deaths and rivaroxaban 5 mg BID primarily reducing MIs
- Net clinical benefit of rivaroxaban
- Mortality results and whether a mortality claim is warranted

10 Attachment 1: Pertinent Presubmission Regulatory Activity

The pertinent presubmission regulatory activity for NDA 202,439 is displayed in Table 41.

Table 41. Summary of Presubmission Regulatory Activity

Date	Event
June 30, 2008	End of Phase 2 Meeting for IND 75,931
August 29, 2008	Original Protocol submitted
September 12, 2008	Advice Letter – "30 day censoring rule can be utilized for the primary analysis"
October 15, 2008	Protocol Amendment #1 submitted
November 26, 2008	First Patient Randomized
June 19, 2009	Original SAP submitted
July 8, 2009	Statistical Review/Both strategies (data combined across strata and Stratum 2 only) need to be successful to make a claim for the Stratum 2 population/Efficacy analysis should be ITT, not mITT
July 15, 2009	Statistical Advice Letter sent to Sponsor
August 5, 2009	Fast Track Designation
August 25, 2009	Protocol Amendment #2 submitted
October 5, 2010	SAP Amendment #1 submitted
January 22, 2011	Last Patient Randomized
May 10, 2011	Pre-NDA Meeting
June 3, 2011	Global Treatment End Date (12:01 a.m.)
September 15, 2011	SAP Amendment #2 submitted
September 19, 2011	Final Patient Contact
September 24, 2011	Database Locked
October 14, 2011	Statistical Review/Sensitivity Analyses with Sites 091001, 091019, and 091026 would be conducted
October 18, 2011	ATLAS Topline Results Meeting with Sponsor
December 29, 2011	NDA Submission (202,439)
ITT: intent-to-treat; mITT: modified intent-to-treat; NDA: New Drug Application; SAP: statistical analysis plan	

11 Attachment 2: Tabular Listing of Clinical Studies

Study Type Study ID EudraCT Number First Patient First Visit / Completion date (day Mon year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
Healthy Subject Pharmacokinetic and Initial Tolerability Studies						
BAY 59-7939/12570 Eudra CT: 2007-003990-22 FPFV: 10 Nov 2010/ Completion: 22 Dec 2010 Completed	Germany: 1 Center	Phase 1 Randomized, open-label, non-controlled, 3-way crossover study to assess the PK, safety, and tolerability of an ER formulation of riva with and without food in comparison to the IR formulation in healthy male subjects	Planned: 12 Enrolled: 12 Randomized: 12	Riva 12 mg modified ER tablet E 202 (Oral) and 10 mg IR tablet (Oral) Single dose 12 mg ER formulation in fed and fasted condition; single dose 10 mg IR formulation in fasted condition	12 mg ER fed: 12; 12 mg ER fasted: 11; 10 mg IR fasted: 11	Full CSR Issued on 21 Jul 2011 Report No.: PH-36590 Module 5.3.3.1
BAY 59-7939/12571 Eudra CT: 2010-022937-27 FPFV: 19 Nov 2010 Completion: 12 Jan 2011 Completed	Germany 1 Center	Phase 1 Randomized, open label, non-controlled, 3-way crossover study to assess the PK, safety, and tolerability of an ER formulation of riva (GITS) with and without food in comparison to the IR formulation in healthy male subjects	Planned: 12 Enrolled: 11 Randomized: 11	Riva 12 mg modified ER tablet (GITS 329) (oral) and 10 mg coated IR tablet (oral) Single dose 12 mg GITS ER formulation in fed and fasted condition; single dose 10 mg IR formulation in fasted condition	12 mg ER fed: 11; 12 mg ER fasted: 11; 10 mg IR fasted: 11	Full CSR Issued on 19 Aug 2011 Report No.: PH-36612 Module 5.3.3.1

Study Type Study ID EudraCT Number First Patient First Visit / Completion date (day Mon year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
BAY 59-7939/12361 Eudra CT: 2010-022277-33 FPFV: 11 Nov 2010 Completion: Feb 10 2011 Completed	Germany 1 Center	Phase 1 Randomized, non-blind, non-controlled, 3-way crossover study to assess the PK, safety, and tolerability of different dose strengths of riva (2.5mg, 5 mg, 10 mg) in healthy male subjects	Planned: 24 Enrolled: 24 Randomized: 24	Riva 2.5 mg, 5 mg and 10 mg IR film-coated tablets (Oral) Single dose	Riva 2.5 mg: 24 5 mg: 23 10 mg: 24	Full CSR Issued on 04 Aug 2011 Report No.: PH-36607 Module 5.3.3.1
Extrinsic Factor Pharmacokinetic Studies						
Study 12606 Eudra CT: 2010-020237-70 FPFV: 11 Jun 2010/ Completion: 16 Aug 2010 Completed	Germany: 1 Center	Phase 1 Randomized, open-label, 2-fold cross-over study to investigate the influence of multiple doses of 400 mg fluconazole on safety, tolerability, and PK of a single oral dose of 20 mg riva in healthy male subjects	Planned: 14 Enrolled: 14 Randomized: 14	Study drug: Riva 20 mg IR tablet (Oral) 2 single doses (Period 1 and 2 on Day 0d) Interacting drug: Fluconazole (Diflucan®) (Oral) 200 mg capsules 2 capsules (400 mg) once daily for 6 days in Period 2 (Day -4 to 1)	Treatment A (riva alone): 13; Treatment B (riva + fluconazole): 13	Full CSR Issued on 22 Nov 2010 Report No.: PH-36370 NDA 202,439/seq0048/ Module 5.3.3.4

Study Type Study ID EudraCT Number First Patient First Visit / Completion date (day Mon year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
Healthy Subject Pharmacodynamic and Pharmacokinetic/ Pharmacodynamic Studies						
Study 14883 FPFV: 25 Jun 2010/ Completion: 14 Sep 2010 Completed	Japan 1 Center	Phase 1 Randomized, placebo-controlled, parallel-group study in Japanese healthy male subjects to investi-gate the pharmaco-dynamics and pharmaco-kinetics during the switching procedure from warfarin to riva.	Planned: 36 Enrolled: 36 Randomized: 36	Study drug: Riva (oral) 15 mg once daily on Days 0-3 Warfarin (oral) 5 mg or INR-adjusted lower dose od on Days -6 and -5, 0.5 to 10 mg depending on IRN, od on Days -4 to -1. Vitamin K (oral) 10 mg od on Day 5	Treatment A (warfarin + riva): 12 Treatment B (wafarin+placebo): 12 Treatment C (riva): 12	Full CSR Issued on 08 Feb 2011 Report No.: A51960 NDA 202,439/seq0048/ Module 5.3.4.1
Patient Pharmacodynamic and Pharmacokinetic/Pharmacodynamic Studies						
RIVAROXCPK3001 FPFV: 22 Mar 2010/ Completion: 17 Dec 2010 Completed	United States 5 Sites	Phase 3B An open-label pharmacodynamic study of initiation of riva following low molecular weight heparin (LMWH) for venous thrombo-embolism (VTE) prophylaxis after total joint replacement	Planned: 50 Enrolled: 56 Randomized: NA	Riva 10 mg (Oral) 10 mg once daily The total duration of combined VTE prophylaxis was variable, but may not exceed 35 days (for THR) or 14 days (for TKR)	53 subjects received riva 10 mg	Full CSR Issued on 19 May 2011 Report No.: EDMS-ERI-25525015 Module 5.3.4.2

Study Type Study ID EudraCT Number First Patient First Visit / Completion date (day Mon year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
Efficacy and Safety Controlled Clinical Studies						
RIVAROXACS3001 (ATLAS ACS2 TIMI 51) Eudra CT: 2008-002708-25 FPFV: 26 Nov 2008 / Completion: 19 Sep 2011 Completed Synopsis		Phase 3 A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Riva in Subjects With a Recent Acute Coronary Syndrome, in addition to ASA alone, or ASA plus a thienopyridine	Planned: 15,500 Screened: 15,932 Enrolled: 15,526 Randomized: 15,528	Riva 2.5 mg, 5 mg (Oral) 2.5 mg or 5 mg bid, in addition to ASA along or ASA plus thienopyrid This was an event driven study. Mean durations were: 2.5 mg: 397.0 days 5 mg: 376.5 days	Placebo: 5,113 Riva 2.5 mg bid: 5,115 Riva 5 mg bid: 5,110	Full CSR Issued on 18 November 2011 Report No.: EDMS-ERI-26178705:1.0 Module 5.3.5.1
39039039ACS2001 (ATLAS ACS TIMI 46, Impact 11898) Eudra CT: 2006-004449-40 FPFV: 17 Nov 2006/ Completion: 19 Sep 2008 Completed Synopsis	27 Countries, 297 Centers	Phase 2 Randomized, double-blind, placebo-controlled, multicenter, dose-escalation and dose-confirmation study to evaluate the safety and efficacy of riva in combination with aspirin alone or with aspirin and a thienopyridine in subjects with acute coronary syndromes	Planned: 3600 to 3825 Screened: 3576 Randomized: 3491	Riva 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg IR tablets (Oral) TDD levels of 5 mg, 10mg, 15mg and 20mg as od or bid doses, in addition to ASA along or ASA plus thienopyridie The planned duration for all dose levels was 6 months	Placebo: 1153 TDD 5 mg: 307 TDD 10 mg: 1046 TDD 15 mg: 353 TDD 20 mg: 603	Full CSR Issued on 1 May 2009 Report No.: EDMS-PSDB-7122709:2.0 Module 5.3.5.1

Study Type						
Study ID EudraCT Number First Patient First Visit / Completion date (day Mon year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
Other Clinical Studies						
BAY 59-7939 /12839 (MAGELLaN) Eudra CT: 2007-004614-14 FPFV: 04 Dec 2007/ Completion: 24 Nov 2010 Completed	52 Countries, 562 Centers	Phase 3 Multicenter, randomized, parallel group efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically ill patients comparing riva with enox	Planned: 7190 to 8220 Screened: 8428 Randomized: 8101	Study drug: Riva 10 mg tablet (Oral) od for 35 days (29-41 days, inclusive for efficacy analyses) Comparator: Enox 40 mg sc (Injection) od for 10 days (6-15 days of treatment, inclusive, for efficacy analyses)	Rivaroxaban: 3997 Enox: 4001	Full CSR Issued on May 18 2011 Report No.: A 51599 Module 5.3.5.4
Ongoing – Clinical Studies						
RIVAROXACS1001	NA	Phase 1 An open-label study to estimate the effect of multiple doses of erythromycin on the PK, PD and safety of a single dose of riva in subjects with renal impairment and normal renal function	Planned: 24, 8 each with normal renal function, mild renal impair-ment and moderate renal impairment	Study drug: Riva 5 mg and 10 mg (Oral) Interacting drug: Erythromycin 500 mg (Oral) Treatment A: single dose 10 mg Riva; Treatment B: erythromycin 500 mg 6 days plus single dose 5 mg riva; Treatment C: erythromycin 500 mg 6 days plus single dose 10 mg riva	Planned: Treatment A: 24 Treatment B: 16 (subjects with renal impairment only) Treatment C: 24	Protocol Module 5.3.3.4

Study Type						
Study ID EudraCT Number First Patient First Visit / Completion date (day Mon year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
13238	NA	Phase 2a Multicenter, cohort study evaluating population PK/PD of an adapted riva dose regimen in patients with acute, proximal DVT or acute PE who concomitantly use a strong CYP 3A4 inducer for the entire 3-month study duration	Planned: 50	Riva (Oral) The first 3 weeks: riva 30 mg bid; followed by riva 20 mg bid, with overall duration 3 months	Planned: 50 subjects to be treated with riva.	Protocol NDA 202,439/seq0000/ Module 5.3.5.4
EINSTEIN PE (11702)	NA	Phase 3 Multi-center, randomized, OL, parallel-group, active-controlled, event-driven non-inferiority study in patients with confirmed acute symptomatic PE with or without symptomatic DVT	Approximately 2900 subjects with PE are planned, 400 subjects are required for the dose confirmation phase	Study drug: Riva 15 mg and 20 mg (Oral) 15 mg bid for 3 weeks, followed by 20 mg od/3, 6 or 12 months (determined by the investigator individually); Comparator: Enox/VKA	Planned: 2900 subjects to be randomized to receive riva or enox/VKA	Protocol NDA 202,439/seq0000/ Module 5.3.5.4

Study ID EudraCT Number First Patient First Visit / Completion date (day Mon year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
14397	NA	Phase 3 Randomized, double-blind, parallel-group, active-controlled, dose-confirmatory bridging study for VTE prevention in patients undergoing elective THR.	Planned: 400	Study drug: Riva 5 mg, 7.5 mg and 10 mg tablet (Oral) od for 34-35 (± 4) days Comparator: Enox: 20 mg (2000 IU) (sc injection) bid 6-7 (± 2) days	Planned: 400 subjects to be randomized to 4 treatment groups: Riva 5 mg, Riva 7.5 mg Riva 10 mg Enox 20 mg	Protocol NDA 202,439/seq0048/ Module 5.3.5.4
14398	NA	Phase 3 Randomized, double-blind, parallel-group, active-controlled, dose-confirmatory bridging study for VTE prevention in patients undergoing elective TKR	Planned: 300	Study drug: Riva 5 mg, 7.5 mg and 10 mg tablet (Oral) od for 11-12 days (± 2 days) Comparator: Enox: 20 mg (2000 IU) (sc injection) bid for 10-11 days (± 2 days)	Planned: 300 subjects to be randomized to 4 treatment groups: Riva 5 mg, Riva 7.5 mg Riva 10 mg Enox 20 mg	Protocol NDA 202,439/seq0048/ Module 5.3.5.4
12892	NA	Phase 1 Multicenter, open –label, single dose, non-controlled pilot study in pediatric subjects with VTE	Planned: 8 to 12 subjects in each of the following age groups: 12 to <18 years; 6 to <12 years; 2 to <6 years 6 m to <2 years	Riva 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg tablet or suspension (Oral) Weight/age dependent exposure equivalent to 10mg and 20 mg riva in adults Single dose in fed condition	Planned: 4-6 subjects in each dose group of each age group.	Protocol NDA 202,439/seq0048/ Module 5.3.4.1

Study Type						
Study ID EudraCT Number First Patient First Visit / Completion date (day Mon year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
Ongoing – Post-marketing Studies						
Xamos (13802)	NA	Phase 4 Non-interventional, observational cohort study; to collect data on identified and potential safety risks on the use of riva and other pharmacologic agents in the prevention of VTE in elective hip or knee arthroplasty in clinical practice	Up to 15,000 patients ≥18 years who have undergone elective hip or knee arthroplasty and are using pharmacologic VTE prophylaxis treatment in clinical practice are planned to enroll.	This is a non-interventional study, the decision on the type, duration and dose of drug used for VTE prophylaxis is solely at the discretion of the attending physician.	The study is planned to collect data from 7,500 patients receiving current standard of care drug therapy and 7,500 patients receiving riva.	Protocol NDA 202,439/seq0000/ Module 5.3.6

KEY: 4MSU=4-Month Safety Update; ASA= acetylsalicylic acid; bid=twice a day; CRF=case report form; CRT=case report tabulation; ER=extended release; FPFV=First Patient First Visit; IR= immediate release; m=month; NA=not available or not applicable; PD=pharmacodynamics; od=once daily; PK=pharmacokinetics; riva=rivaroxaban; sc=subcutaneous; enox= enoxaparin; TDD=total daily dose; THR=total hip replacement; VTE=venous thromboembolism

Source: Clinical Study Report, Module 5.2, Tabular Listing of Clinical Studies

12 Attachment 3: Additional Protocol and Amendment Information (ATLAS ACS 2 TIMI 51 Trial)

Protocol and Amendments (A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects With a Recent Acute Coronary Syndrome) (The ATLAS ACS 2 TIMI 51 Trial (The second trial of Anti-Xa Therapy to Lower cardiovascular events in Addition to standard therapy in Subjects with Acute Coronary Syndrome)

The review was based on the original protocol (dated August 20, 2008) submitted to IND 75931on August 29, 2008 (SDN 536), Protocol Amendment INT-1 (dated September 22, 2008) submitted on October 15, 2008 (SDN 586), and Protocol Amendment INT-2 (dated August 25, 2009) submitted on September 11, 2009 (SDN 994).

Objectives

Primary Objective

The primary objective was to determine whether rivaroxaban in addition to standard care reduces the risk of the composite of cardiovascular (CV) death, myocardial infarction (MI), or stroke in subjects with a recent ACS compared with placebo in addition to standard care.

Secondary Objectives

The secondary objectives were

- To determine whether rivaroxaban reduces the risk of the composite of all cause death, MI, or stroke in subjects with a recent ACS compared with placebo in addition to standard care
- To examine the effect of rivaroxaban on net clinical outcome, defined as the composite of CV death, MI, ischemic stroke, or a Thrombolysis in Myocardial Infarction (TIMI) major bleeding event not associated with coronary artery bypass graft (CABG) surgery
- To determine whether rivaroxaban reduces the risk of the composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization in subjects with a recent ACS compared with placebo in addition to standard care
- To determine whether rivaroxaban reduces the risk of the composite of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalization in subjects with a recent ACS compared with placebo in addition to standard care

Safety Objectives
The safety objectives were

- To assess TIMI major bleeding events not associated with CABG surgery as the primary safety endpoint
- To assess overall safety by examining other bleeding events, serious adverse events, adverse events leading to discontinuation of study drug, and adverse events of special interest

Exploratory Objectives
The exploratory objectives of this study were:

- To collect medical resource utilization (MRU) data during the clinical status review and to collect EuroQol (EQ-5D) data in a subset of subjects. The EQ-5D is being collected to confirm the burden of illness in the ACS study population and the increased burden of illness following a secondary event. The EQ-5D data will be incorporated into economic modeling, which will be performed and reported separately from this study.

Hypothesis
The study hypothesis was that treatment with rivaroxaban in addition to standard care was superior to treatment with placebo in addition to standard care in reducing the risk of CV death, MI, or stroke in subjects with a recent ACS.

Inclusion Criteria
Subjects must have satisfied the following criteria for study enrollment:

- Man or woman 18 years of age or older
- Currently receiving ASA therapy (75 to 100 mg/day) alone or in combination with a thienopyridine (clopidogrel or ticlopidine per national dosing recommendation) (Amendment 1)
- Have been hospitalized for symptoms suggestive of ACS that lasted at least 10 minutes at rest, and occurred 48 hours or less before hospital presentation and have a diagnosis of:

    - **STEMI**
      Elevation of ST-segment more than 0.1 millivolt (mV) in 2 or more continuous ECG leads, or new left bundle branch block, or ST-segment depression 0.1 mV or greater in 2 of the precordial leads V1-V4 with evidence suggestive of true posterior infarction, all with elevated biomarkers of myocardial necrosis (creatinine kinase-muscle and brain isoenzyme [CK-MB] or troponin)

    - **NSTEMI**
      Transient ST-segment elevation, or ST-segment depression, or T-wave changes consistent with myocardial ischemia along with elevated biomarkers of myocardial necrosis (creatinine kinase-muscle and brain isoenzyme [CK-MB] or troponin)

In Amendment 2 (dated August 6, 2009), NSTEMI entry criteria were revised as follows:

- Elevated biomarkers of myocardial necrosis (creatinine kinase-muscle and brain isoenzyme [CK-MB] or troponin) plus 1 of the following:
  - Transient ST-segment elevation, or ST-segment depression, or T-wave changes consistent with myocardial ischemia, or
  - Identification of a culprit lesion at coronary angiography demonstrating recent, active intracoronary athero-thrombosis (for example, thrombus or an ulcerated plaque)

o **UA with at least 1 of the following:**

- Transient or persistent ST-segment deviation 0.1 mV or greater in 1 or more ECG leads
- TIMI risk score of ≥ 3

In Amendment 2, UA entry criteria were revised as follows:

UA with at least 1 of the following:

- Transient or persistent ST-segment deviation 0.1 mV or greater in 1 or more ECG leads
  or
- TIMI risk score of ≥ 4

Table 42. TIMI Risk Scores

TIMI Risk Scores[18,19]	
UA/NSTEMI	
Age ≥65 years	1 point
ST deviation ≥ 0.5 mm	1 point
≥3 CAD Risk Factors (elevated cholesterol, family history of heart disease, hypertension, diabetes mellitus, smoking)	1 point
ASA in last 7 days	1 point
≥2 anginal events ≤24 hours	1 point
Prior CAD (cath stenosis >50%)	1 point
Elevated CK-MB or troponin	1 point
STEMI	
Age ≥75 years	3 points
Age 56-74 years	2 points
Diabetes mellitus, hypertension, or angina	1 point
Systolic blood pressure <100 mmHg	3 points
Heart rate >100 bpm	2 points
Killip Class II-IV	2 points
Weight <67 kg	1 point
Anterior STE or LBBB	1 point
Time to treatment >4 hours	1 point

(Protocol, Amendment 2 (dated August 6, 2009), Attachment 2, page 118)

- Subjects who are 18 to 54 years of age inclusive must also have either diabetes mellitus or a prior MI in addition to the presenting ACS event
- Women must be:
  - Postmenopausal (for at least 2 years), or
  - Surgically sterile, (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or
  - Abstinent (at the discretion of the investigator/per local regulations), or
  - If sexually active, be practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method, male partner sterilization) as local regulations permit, before entry, and must agree to continue to use the same method of contraception throughout the study
  - Women of childbearing potential must have a negative urine β-human chorionic gonadotropin (β-hCG) pregnancy test at screening. Serum pregnancy testing may be performed if required by local regulation.
  - Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are wiling to participate in the study

Exclusion Criteria
Subjects who meet any of the following criteria will be excluded from the study:

Bleeding Risk
- Any condition that, in the opinion of the investigator, contraindicates anticoagulant therapy or would have an unacceptable risk of bleeding, such as, but not limited to, the following:
  - Active internal bleeding, clinically significant bleeding, bleeding at a noncompressible site, or bleeding diathesis within 30 days of randomization
  - Platelet count < 90,000/μL at screening
  - History of intracranial hemorrhage
  - Major surgery, biopsy of a parenchymal organ, or serious trauma (including head trauma) within 30 days before randomization
  - Clinically significant gastrointestinal bleeding within 12 months before randomization
  - Have an International Normalized Ratio (INR) known to be > 1.5 at the time of screening
  - Abciximab bolus or infusion within the past 8 hours, or an eptifibatide or tirofiban bolus or infusion within the past 2 hours before randomization
  - Any other condition known to increase the risk of bleeding

Severe concomitant diseases such as:
- Cardiogenic shock at the time of randomization
- Ventricular arrhythmias refractory to treatment at the time of randomization
- Calculated creatinine clearance < 30 mL/min at screening

- Known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis), or liver function test (LFT) abnormalities (confirmed with repeat testing) which would require study drug discontinuation, i.e., ALT > 5 times the ULN or ALT > 3 times the ULN plus total bilirubin > 2 times the ULN)
- A prior stroke in a subject currently receiving ASA plus a thienopyridine (Note: Subjects with a prior stroke receiving ASA therapy alone are eligible for inclusion in the study)

  Amendment 2 revised this exclusion criterion to:
  "A prior ischemic stroke or TIA in subjects who are planned to be included in stratum 2 (ASA plus thienopyridine). (Note: Subjects with a prior ischemic stroke or TIA are eligible for inclusion in the study only if they are intended to be treated with ASA only). Subjects with a prior hemorrhagic stroke are excluded completely from the study.

- Anemia (i.e., hemoglobin < 10 g/dL) at screening
- Known clinical history of HIV infection at screening
- Substance abuse (drug or alcohol) problem within the previous 6 months)
- Any severe condition that would limit life expectancy to less than 6 months

General:

- Systemic treatment with strong CYP 3A4 and P-gp inhibitors (e.g., certain azoleantimycotics, such as ketoconazole and HIV-protease inhibitors, such as ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp.
- Allergy or hypersensitivity to any component of rivaroxaban or placebo excipients (includes lactose, microcrystalline cellulose, magnesium stearate, hypromellose, macrogol, croscarmellose sodium, sodium lauryl sulfate, titanium oxide)
- Known aspirin allergy
- Atrial fibrillation or other condition requiring anticoagulation (e.g., warfarin sodium)

  Amendment 2 revised this exclusion criterion as follows:
  "Atrial fibrillation excluded except for subjects younger than 60 years of age who have no clinical or echocardiographic evidence of cardiopulmonary disease and who had only a single episode of atrial fibrillation that occurred more than 2 years ago."

- Use of disallowed therapies (see Prohibited Therapy)
- Received an investigational drug or used an investigational medical device within 30 days before the planned start of treatment, or are currently enrolled in an investigational study
- Anticipated need for chronic (more than 4 weeks) therapy with non-steroidal anti-inflammatory drugs (NSAIDs)
- Is pregnant or breast-feeding or planning to become pregnant during the study
- Have previously completed or withdrawn from this study

- Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements
- Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator

Allowed Therapy
All subjects were to receive oral, antiplatelet therapy of either low-dose ASA (75 to 100 mg/day) or, as considered medically appropriate by the managing clinician, combination therapy of ASA and a thienopyridine. The daily dose of the thienopyridine was to follow the national or local prescribing instructions. If required, a loading dose of the thienopyridine could be used according to routine practice. The daily maintenance dose of clopidogrel and ticlopidine was not to exceed 75 mg daily and 250 mg twice daily, respectively. The duration of dual antiplatelet therapy was at the discretion of the investigator and could depend on whether a subject received a bare metal stent or drug eluting stent.

All other concomitant medication was at the discretion of the managing clinician, including the use of H-2 antagonists or proton pump inhibitors. Non-steroidal anti-inflammatory agents could be used on a temporary basis, but were to be avoided for chronic use.

Prohibited Therapy
The following concomitant therapies were prohibited:
- ASA doses exceeding 100 mg/day after randomization
- Systemic treatment with strong CYP 3A4 and P-gp inhibitors (e.g., certain azoleantimycotics, such as ketoconazole and HIV-protease inhibitors, such as ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp.
- Chronic use of antiplatelet medication (other than ASA, clopidogrel and ticlopidine) or anticoagulant therapy (warfarin sodium or VKA).

These prohibited therapies could be administered temporarily if study drug was temporarily discontinued first. Study drug could be restarted after the prohibited therapy was discontinued, following an adequate wash-out period per the investigator's discretion.

13 Attachment 4: Sites Excluded from the Sponsor's Efficacy Analyses (Sites 091001, 091019, and 091026)

Table 43. Reviewer Analysis of Primary Efficacy Endpoint Events and Non-Cardiovascular Death (Sites 091001, 091019, and 091026)

Site	Subject	Stratum	Treatment	Event	Reviewer Comments
091001	300394	2	Rivaroxaban 5 mg BID	Other Cardiac Ischemic Event	
	300700	2	Rivaroxaban 5 mg BID	Severe Recurrent Ischemia Requiring Hospitalization	
	300801	2	Rivaroxaban 5 mg BID	CV Death	Agree.
	302926	2	Placebo	CV Death	Agree.
	303207	2	Placebo	Other Cardiac Ischemic Event	
	303580	2	Rivaroxaban 5 mg BID	Non-CV Death	Agree.
	304118	2	Rivaroxaban 5 mg BID	Other Cardiac Ischemic Event	
	305339	2	Rivaroxaban 2.5 mg BID	MI	Agree.
	305904	2	Rivaroxaban 5 mg BID	CV Death	Agree.
	308003	1	Placebo	Severe Recurrent Ischemia Requiring Hospitalization	
	308864	2	Rivaroxaban 5 mg BID	Severe Recurrent Ischemia Requiring Hospitalization	
	309351	2	Rivaroxaban 5 mg BID	Other Cardiac Ischemic Event	
	312422	2	Placebo	Severe Recurrent Ischemia Requiring Revascularization	
091019	300766	2	Rivaroxaban 5 mg BID	Severe Recurrent Ischemia Requiring Hospitalization	
	302841	2	Rivaroxaban 2.5 mg BID	Other Cardiac Ischemic Event	
	305151	2	Rivaroxaban 5 mg BID	MI	Agree.

Site	Subject	Stratum	Treatment	Event	Reviewer Comments
	305360	2	Rivaroxaban 5 mg BID	MI	Not all ECGs have dates/times. Pt definitely had a recurrent MI, as the cardiac biomarkers were positive. Unclear which ECGs corresponded to 12/22/2009 visit. One was marked as 12/22/2009, but it looked like this ECG could have been from the index AWMI on 10/22/2009 treated with thrombolytics.
	307728	2	Placebo	Other Cardiac Ischemic Event	
091026	302532	2	Rivaroxaban 5 mg BID	CV Death (Stent Thrombosis)	Agree. This pt did not undergo revascularization for index event. So if pt had a stent, it was placed at a different time.
	304178	2	Placebo	CV Death	Agree.
	306949	2	Rivaroxaban 5 mg BID	CV Death	Agree.
	310401	2	Rivaroxaban 2.5 mg BID	CV Death (Stent Thrombosis)	Agree.
BID: twice daily; CV: cardiovascular; ECG: electrocardiogram; MI: myocardial infarction					

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/s/

KAREN A HICKS
04/30/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #/Serial #:	202-439
DRUG NAME:	Rivaroxaban
INDICATION:	Reduce the risk of thrombotic CV events in ACS
APPLICANT:	Janssen Research & Development
DATE OF RECEIPT:	12/31/2011
REVIEW PRIORITY:	Priority
BIOMETRICS DIVISION:	Division of Biometrics I
STATISTICAL REVIEWER:	Steve Bai, Ph.D.
CONCURRENT REVIEWER:	James Hung, Ph.D. Director DBI
MEDICAL DIVISION:	Division of Cardiovascular and Renal Products
CLINICAL TEAM:	Karen Hicks, MD
	Thomas Marciniak, MD
PROJECT MANAGER:	Michael Monteleone

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1 EXECUTIVE SUMMARY

The following conclusions can be drawn from the ATLAS ACS 2 TIMI 51 trial:

- In All Strata, including the subjects with the use of ASA and a thienopyridine plus ASA, Rivaroxaban was effective in reducing the occurrence of the composite primary endpoint of cardiovascular death, myocardial infarction or stroke compared with placebo in subjects with a recent ACS. The combined Rivaroxaban dose, the 2.5 mg b.i.d. and the 5 mg b.i.d. were effective in reducing the occurrence of the primary efficacy endpoint.
- In Stratum 2, including the subjects only with the use a thienopyridine plus ASA, Rivaroxaban was effective in reducing the occurrence of the composite primary endpoint of cardiovascular death, myocardial infarction or stroke compared with placebo in subjects with a recent ACS. The combined Rivaroxaban doses and the 2.5 mg b.i.d. were effective in reducing the occurrence of the primary efficacy endpoint.
- The above findings were largely driven by the reduction of CV deaths particularly in the 2.5 mg b.i.d. dose group. The 2.5 mg b.i.d. dose of Rivaroxaban was also nominally statistically significant in reducing the incidence of all cause deaths in All Strata and Stratum 2. However, the 5.0 mg b.i.d was not shown effective and appeared to have little effect for the reduction of all cause deaths. Furthermore, the reduction of all cause deaths was not statistically robust for the combined doses. The board line effectiveness finding depends on which analysis sets are used and whether 3 Indian sites to be excluded from the analyses.

2 INTRODUCTION

This is a statistical review of NDA 202439/0125 investigating the efficacy of Rivaroxaban as prevention of thrombotic CV events in patients with acute coronary syndrome (ACS) [STEMI, NSTEMI or UA] in combination with aspirin alone or with aspirin plus a thienopyridine (clopidogrel or ticlopidine).

The Rivaroxaban ACS program includes the following 2 clinical studies:

1. A pivotal Phase 3 efficacy and safety study ATLAS ACS 2 TIMI 51 (the second trial of Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome), Study number RIVAROXACS3001 (or BAY-59-7939/13194); and
2. A dose-escalation, dose-confirmation Phase 2 safety and efficacy study ATLAS ACS TIMI 46 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome), Study number 39039039ACS2001 (or BAY-59-7939/11898).

This statistical review will focus solely on the pivotal phase 3 ATLAS trial.

2.1 Overview

Coronary heart disease (CHD) is an extremely common clinical and pathological condition. The incidence and prevalence rates of CHD remain high throughout the developed world. In the

U.S., the American Heart Association reports that the prevalence of CHD in adults ≥20 years of age is 7.0%; CHD prevalence is 8.3% for men and 6.1% for women.20 Approximately 785,000 Americans each year will have a coronary event, and approximately 470,000 will have a recurrent event. CHD is the major cause of death in adults in the U.S. and in most countries in Europe.

Because of difficulties inherent with warfarin monitoring, such as variations in dose response, the need for patient compliance in the monitoring of coagulation parameters and adjustment of dosing, multiple drug and food interactions, and a heightened risk for bleeding, especially when administered in combination with ASA therapy, there remains an unmet medical need for the development of safer, efficacious, and convenient oral anticoagulants that do not depend on vitamin K antagonism for the treatment of subjects with ACS. One such promising class of oral anticoagulants is the Factor Xa (FXa) inhibitors. Rivaroxaban is a potent and highly selective direct FXa inhibitor. Selective inhibition of FXa by Rivaroxaban reduces thrombin generation while still allowing some generation of thrombin to provide a margin of control over hemostasis.

In this submission, the sponsor is seeking approval for Rivaroxaban for the prevention of CV events in patients with acute coronary syndrome (ACS). The efficacy and safety of Rivaroxaban in this ACS program have been studied in two clinical studies:

Table 1 List of pivotal studies

Study	Phase	Objectives	# of Subjects	Study Drug(s)
ATLAS ACS 2 TIMI 51	Phase 3	Blind, Placebo- controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Riva in Subjects With a Recent Acute Coronary Syndrome, in addition to ASA alone, or ASA plus a thienopyridine	15, 528	Riva 2.5 mg or 5 mg bid, in addition to ASA along or ASA plus thienopyrid
ATLAS ACS TIMI 46	Phase 2	Randomized, double-blind, placebo-controlled, multicenter, dose-escalation and dose-confirmation study to evaluate the safety and efficacy of riva in combination with aspirin alone or with aspirin and a thienopyridine in subjects with acute coronary syndromes	3491	Riva 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg IR tablets

ATLAS ACS 2 TIMI 51 was adequately powered to be a single pivotal study able to demonstrate the clinical efficacy and safety of Rivaroxaban in patients with a recent ACS. The ATLAS ACS 2 TIMI 51 study overall demonstrated Rivaroxaban to be associated with a significant reduction in CV and all-cause mortality, particularly in the 2.5mg b.i.d. dose group. This review will focus on the efficacy evaluation of ATLAS ACS 2 TIMI 51.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\Cdsesub1\evsprod\NDA202439\0125\m5\datasets.

Data for the pivotal study (TIMI 51) were submitted in SDTM format and associated SAS programs were also provided for the pivotal study (TIMI 51).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There are not any statistical issues with the data or analysis quality. The data files were in SAS transport format. Many files were larger than recommended by the FDA guidance document (50 MB).

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The ATLAS ACS 2 TIMI 51 study was a randomized, double-blind, placebo-controlled, event driven, multicenter study designed to evaluate the efficacy and safety of Rivaroxaban in subjects with a recent ACS (STEMI, NSTEMI, or UA) who were receiving standard care. The study was conducted in 3 phases: a 6-day screening phase, a double-blind treatment phase, and a follow-up phase. The projected date of accrual of at least 983 primary efficacy endpoint events anticipated to be adjudicated as mITT events.

Seven hundred sixty-six sites in 44 countries worldwide randomized subjects in this study. And these countries were grouped into six regions: North America, South America, Western Europe, Eastern Europe, Asia Pacific and Others.

Rivaroxaban was provided as tablets and each tablet contained 2.5 or 5 mg of Rivaroxaban. The comparators were the matching placebo tablets. There were no visible differences between the 2 Rivaroxaban strengths and the matching placebo tablets.

The use of a thienopyridine plus ASA in subjects with ACS is recommended by American College of Cardiology (ACC)/ AHA and European Society of Cardiology (ESC) guidelines and should be considered standard care for subjects with ACS. Subjects whom the investigator intended to treat with ASA plus a thienopyridine were entered into Stratum 2. However, thienopyridine therapy may have been considered unsuitable because of intolerance or allergy, a previous adverse event attributable to a thienopyridine, or because the risk of taking a thienopyridine was considered by the treating physician to outweigh the benefit of taking one, or because of other local standard of care. Subjects whom the investigator intended to treat with ASA only were entered into Stratum 1.

This was an event-driven study. A total of 983 primary efficacy endpoint events were estimated to have approximately 96% power to detect a 22.5% relative reduction (i.e., hazard ratio=0.775) between pooled doses of Rivaroxaban and placebo arms pooled across Both

strata, with a 2- sided type I error rate of 0.05. The total 983 events was estimated based on the sum of the events required at approximately 90% power in each stratum, to detect a 35% RR in Stratum 1 (255 primary efficacy endpoint events) and a 22.5% RR in Stratum 2 (728 primary efficacy endpoint events) comparing combined Rivaroxaban doses and placebo arms.

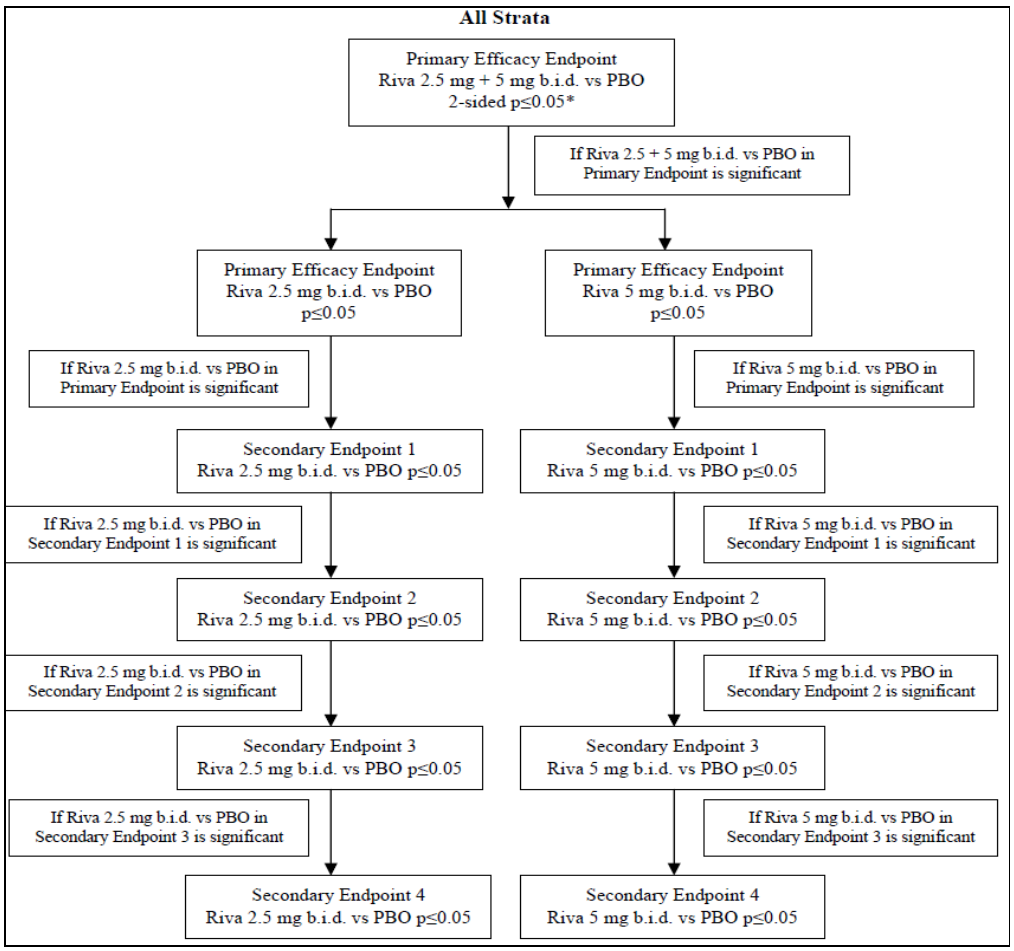
The primary efficacy endpoint was the composite of CV death, MI, or stroke. The primary objective of this study was to show Rivaroxaban in addition to standard care is superior to placebo in terms of reducing the risk of the composite of cardiovascular (CV) death, MI, or stroke in subjects with a recent ACS.

There were four secondary efficacy endpoints:

1. Composite of all-cause death, MI, or stroke
2. Net Clinical Outcome (i.e., composite of CV death, MI, ischemic stroke, or non-CABG TIMI major bleeding event)
3. Composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization
4. Composite of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalization

The statistical analysis plan (SAP) was originated on June 19, 2009, with amendment 1 on October 5, 2008 and amendment 2 on September 15, 2011. Throughout all three documents, the sponsor was consistent about two simultaneous evaluation strategies, which were selected on the basis of differing regulatory requirements and were employed for the primary endpoint analyses. The primary evaluation strategy was based on data combined across both strata (i.e., All Strata). A second evaluation strategy was based on the FDA-recommended approach of combined analyses across both dose regimens in subjects in Stratum 2 only. The detailed strategy is as follow: If the superiority of a dose group was declared for the primary efficacy endpoint, the secondary efficacy endpoints were tested for that dose group, at the same 2-sided significance level of 0.050, in sequential order (i.e., Secondary Efficacy Endpoint 1, 2, 3, etc.). Each subsequent ordered secondary endpoint could be tested only for the doses that were significant for the previous endpoints. If an individual test during any step was not statistically significant, further testing could continue but significance could not be claimed, see Figure 1. The identical testing strategy was also performed on Stratum 2.

Figure 1 Diagram of Statistical Testing Procedure



On July 15, 2009, the agency sent the sponsor a statistical advice letter on several issues of the original SAP. There were three main issues:

1. Agency had concerns with stratum 1 which were expressed at the End of Phase 2 meeting, sponsor needed to make it clear in the SAP that both strategies need to be successful in order to make the claim for the population on Stratum 2.
2. Encouraged sponsor not to spend alpha on the proposed secondary endpoints, because they are similar to the primary endpoint. The likelihood of getting a claim based on the proposed secondary endpoints is low.
3. If the sponsor insisted on the testing of the proposed secondary endpoints, then testing procedure of the SAP may not have control on the family-wise type I error rate. Suppose 1) Riva 5.0 mg BID vs. PBO has an infinite effect in primary endpoint, 2) Riva 2.5 mg BID vs. PBO has zero effect in primary endpoint, and 3) Riva 5.0 mg vs. PBO has zero

effect in the first secondary endpoint. In this scenario, the probability to make type I error can be as large as 10% depending on the correlations between 2) and 3).

However, the sponsor did not attempt to address any of the above comments in the subsequent two amendments. Furthermore, several analysis sets were stipulated in the SAP:

1. Modified Intent-to-Treat (mITT),
2. Intent-to-Treat (ITT)
3. Intent-to-Treat Total (ITT-Total)
4. Treatment-Emergent Safety
5. mITT Approach Safety
6. Safety Observational Period (i.e. including all post baseline events).

The sponsor proposed to perform all efficacy analyses in the MITT analysis set. The agency had advised sponsor to use the ITT analysis set as the primary analysis dataset in the advice letter. However, the sponsor also did not address this issue in any of the following submissions.

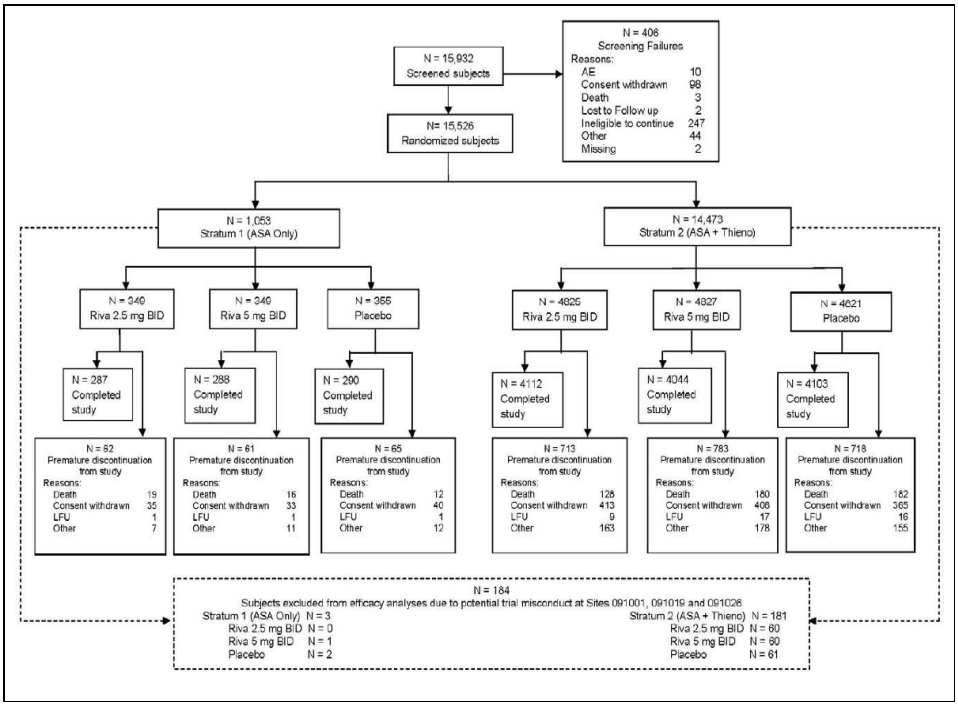
Lastly, one of the major changes in SAP Amendment 2 was the exclusion of 3 Indian sites (091001, 091019, and 091026) from the efficacy analyses due to potential trial misconduct. The agency's response to this change was:

Making late changes to the SAP is problematic, and it may have impact on the interpretation of the study results. Thus sensitivity analyses of including/excluding these sites are expected.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 15,932 subjects were screened for eligibility; 15,526 (97.5%) subjects were randomized and 406 (2.5%) subjects were screening failures. The most frequent reasons for screening failures were "Subject ineligible to continue" (247 [1.6%]) and "Consent withdrawn" (98 [0.6%]). The disposition of subjects randomized into the study is summarized in Figure 2.

Figure 2 Subject Disposition



Baseline and demographics information of the all randomized subjects are provided in Table 2. There were approximately 3 of every 4 subjects were men (74.7%) and the mean age was 61.8 years (range 22 to 98 years). The mean age of subjects was around 62. The majority of subjects were white (73.5%) and 20.8% were Asian. There were relatively few subjects enrolled with moderate to severe renal impairment (1086 [7.1%] subjects with baseline CrCl <50 mL/min). The majority of subjects had CV risk factors, such as hypertension, DM, and history of MI. There were no important imbalances in baseline demographic or disease characteristics among treatment groups.

Table 2 Demographic and Baseline Characteristics (All Randomized Subjects)

	Riva 2.5mg N=5174	**Riva 5.0 mg N=5176**	**Placebo N=5176**	**Total N=15526**
Age				
Mean (SD)	61.8 (9.23)	61.9 (9.03)	61.5 (9.39)	61.8 (9.22)
Median (Q1, Q3)	61.0	61.0	61.0	61.0
Min, Max	25, 91	26, 93	22, 98	22, 98
Sex, n(%)				
Male	3875 (74.9)	3843 (74.2)	3882 (75.0)	11600 (74.7)
Female	1299 (25.1)	1333 (25.8)	1294 (25.0)	3926 (25.3)
Race, n (%)				
White	3798 (73.4)	3815 (73.7)	3796 (73.3)	11409 (73.5)
Black	34 (0.7)	34 (0.7)	39 (0.8)	107 (0.7)
Asian	1099 (21.2)	1055 (20.4)	1075 (20.8)	3229 (20.8)

Other	243 (4.7)	272 (5.3)	264 (5.2)	781 (5.1)
Admitting Diagnosis, n (%)				
STEMI	2601 (50.3)	2584 (49.9)	2632 (50.9)	7817 (50.3)
NSTEMI	1321 (25.5)	1335 (25.8)	1323 (25.6)	3979 (25.6)
UA	1252 (24.2)	1257 (24.3)	1221 (23.6)	3730 (24.0)
Baseline CrCl (mL/min), n (%)				
<30	25 (0.5)	22 (0.4)	30 (0.6)	77 (0.5)
30-50	344 (6.7)	315 (6.2)	350 (6.8)	1009 (6.6)
50-80	1779 (34.8)	1847 (36.2)	1748 (34.1)	5374 (35.0)
>80	2963 (58.0)	2920 (57.2)	2992 (58.4)	8875 (57.9)
Baseline PCI for Index Event				
Yes	3117 (60.2)	3106 (60.0)	3101 (59.9)	9324 (60.1)
Prior MI				
Yes	1363 (26.3)	1403 (27.1)	1415 (27.3)	4181 (26.9)
Prior Stroke				
Yes	100 (1.9)	98 (1.9)	88 (1.7)	286 (1.8)
Prior Hypertension				
Yes	3470 (67.1)	3499 (67.6)	3494 (67.5)	10463 (67.4)
Baseline Diabetes Mellitus				
Yes	1669 (32.3)	1648 (31.8)	1647 (31.8)	4964 (32.0)

3.2.3 Statistical Methodologies

The primary efficacy analysis was the analysis of the first occurrence of the composite of CV death, MI, or stroke. The adjudication of the events was based on the Clinical Endpoint Committee (CEC). The comparisons between treatment groups were performed using a Cox regression analysis with treatment in the model. As prospectively defined in SAP, the mITT analysis set was the primary efficacy analysis set. Further, the subjects from 3 sites (i.e. 091001, 091019, and 091026) were excluded from the efficacy datasets due to potential trial misconduct. However, there weren't consensus on both the definition of analysis set and late stage exclusion of the sites from the agency. The agency recommended ITT analysis set as the primary efficacy set. The difference in event censoring rule between the two analysis sets is listed as the following:

1. mITT: endpoint event that occurred from randomization up to the earlier date of 12:01 am local time on 3 June 2011 [i.e. the global treatment end date], or 30 days after last dose of study drug or 30 days after randomization.
2. ITT: endpoint event that occurred from randomization up to the earlier date of 12:01 am local time on 3 June 2011.

A number of additional efficacy analysis sets were proposed as basis of sensitivity analyses:

- ITT-Total: Endpoint events from randomization up to the last contact date for each subject
- Treatment-Emergent: Endpoint events from first dose up to the date of last dose of study drug plus 2, 7 and 30 days for each subject
- Rebound: potential off-treatment effects, consists of all study drug-treated subjects who had at least 1 day of follow up after the last dose of study drug administration and the endpoint events that occurred after the last dose of study drug administration.

Further, as pre-specified in the SAP, 2 simultaneous evaluation strategies, based on data combined across All Strata and for Stratum 2 only, were used for the efficacy analyses. Both

for the analyses of All Strata and for the analyses of Stratum 2, a set of log-rank tests (stratified by intention to use a thienopyridine for All Strata) in a prespecified hierarchical order were performed for the analyses of the primary and secondary efficacy endpoints. Testing was conducted as outlined in Figure 1.

3.2.4 Results and Conclusions

The following results were based on sponsor specified efficacy analysis set, i.e. mITT excluding Sites 091001, 091019, and 091026. Table 3 summarized the results by treatment group of the primary efficacy analysis, stratified (for All Strata only) by the intention to use a thienopyridine.

In All Strata, the occurrence of primary efficacy endpoint events was significantly reduced in the combined Rivaroxaban groups compared with placebo (HR=0.84 and p-value=0.008). Further, significantly fewer primary efficacy endpoint events were observed individually in the 2.5 mg b.i.d. group (HR=0.84 and p-value=0.020) as well as the 5 mg b.i.d. group (HR=0.85 and p-value=0.028) compared with the placebo group.

In Stratum 2, the result for the combined Rivaroxaban groups was significantly superior to placebo in reducing the occurrence of the composite endpoint of CV death, MI, or stroke (HR= 0.86 and p=0.024). There were significantly fewer primary efficacy endpoint events were observed in the 2.5 mg b.i.d. group compared with the placebo group (HR=0.85 and p-value=0.039). The 5 mg b.i.d. group had numerically fewer events than the placebo group, but it did not reach statistical significance.

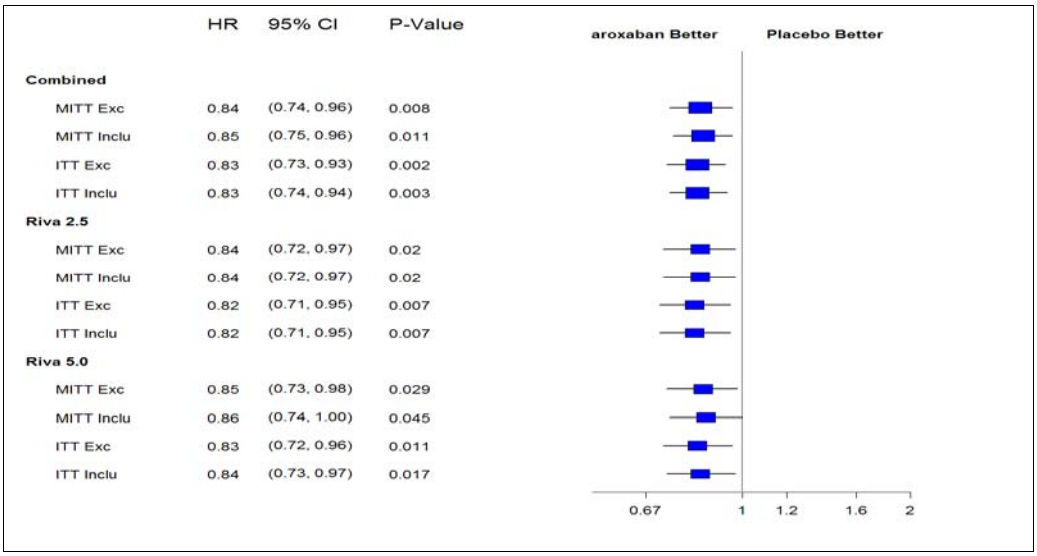
Table 3 Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint as Adjudicated by the CEC (First Occurrence of Cardiovascular Death, MI, Stroke) (mITT excluding Sites 091001, 091019, and 091026)

Stratum	Rivaroxaban			Placebo n/N (%)	2.5 mg vs. Placebo		5.0 mg vs. Placebo		Combined vs. Placebo	
	2.5 mg n/N (%)	5.0 mg n/N (%)	Combined n/N (%)		HR (95% CI)	Log-Rank P-Value	HR (95% CI)	Log-Rank P-Value	HR (95% CI)	Log-Rank P-Value
ALL Strata	313/5114 (6.1)	313/5115 (6.1)	626/10229 (6.1)	376/5113 (7.4)	0.84 (0.72, 0.97)	0.02	0.85 (0.73, 0.98)	0.028	0.84 (0.74, 0.96)	0.008
ASA + Thieno	286/4765 (6.0%)	289/4767 (6.1%)	575/9532 (6%)	340/4760 (7.1%)	0.85 (0.72, 0.992)	0.039	0.87 (0.74, 1.02)	0.076	0.86 (0.75, 0.98)	.0245

[Source: Reviewer's results]

Throughout the entire ACS program, the clear decision on which is the primary efficacy analysis set was never resolved among the choice of All Strata, Stratum 2, and Inclusion/Exclusion of three Indian sites. Figure 3 and Figure 4 display the results of the primary efficacy endpoints in these various analysis sets.

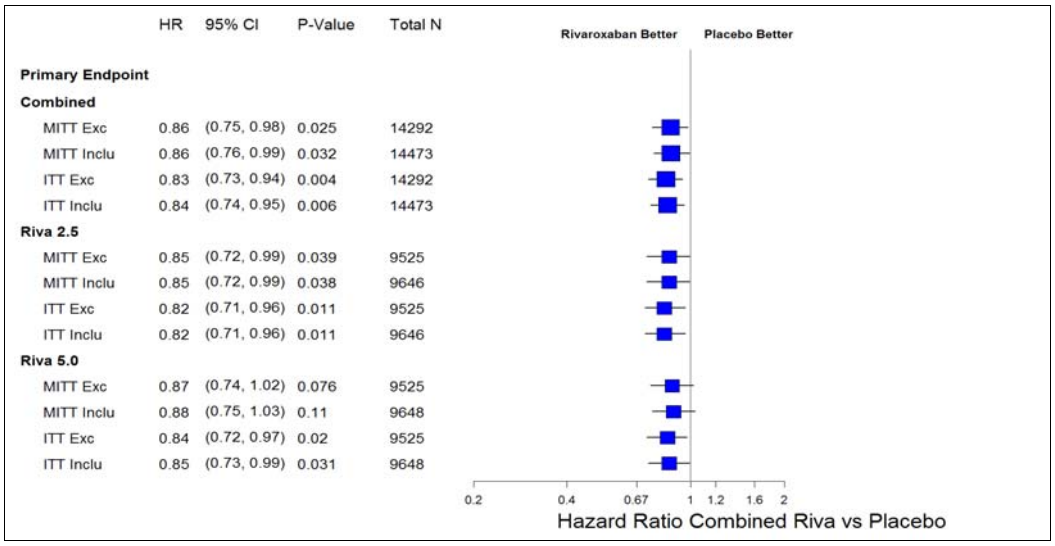
Figure 3 Primary Efficacy Results by Different Analysis Sets in All Strata



[Source: Reviewer's Results]

As we see from the forest plots of Figure 3, for All Strata, the consistent superior findings of Rivaroxaban (combined, 2.5 mg, and 5.0 mg) are observed no matter which analysis sets are used.

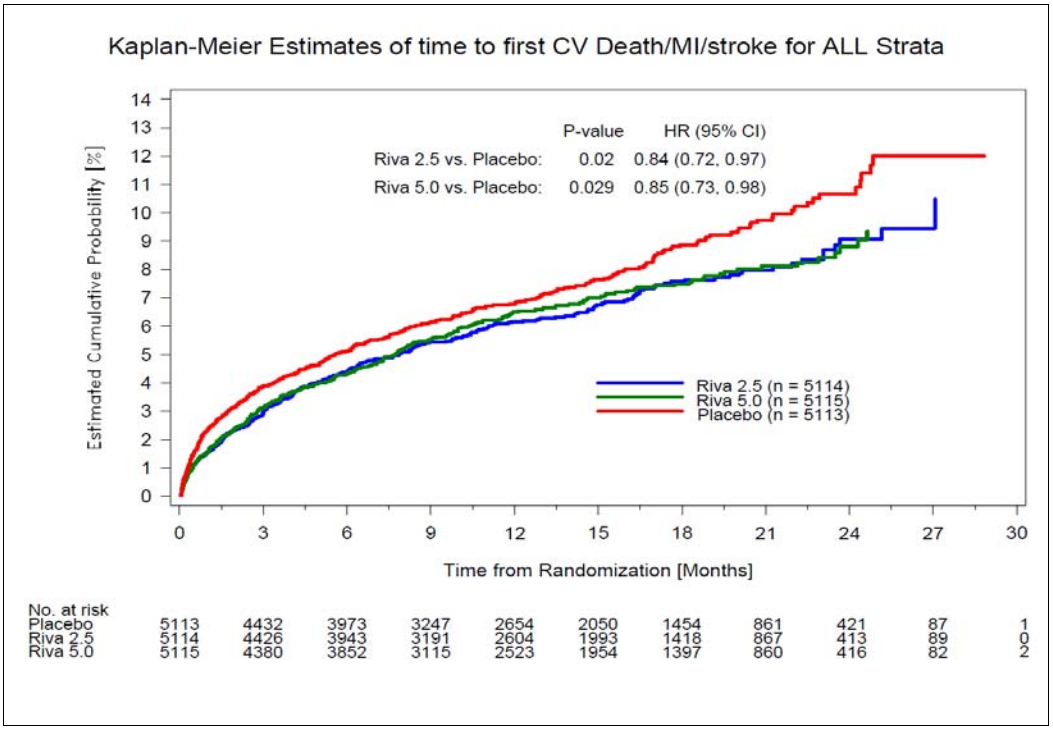
Figure 4 Primary Efficacy Results by Different Analysis Sets in Stratum 2



[Source: Reviewer's Results]

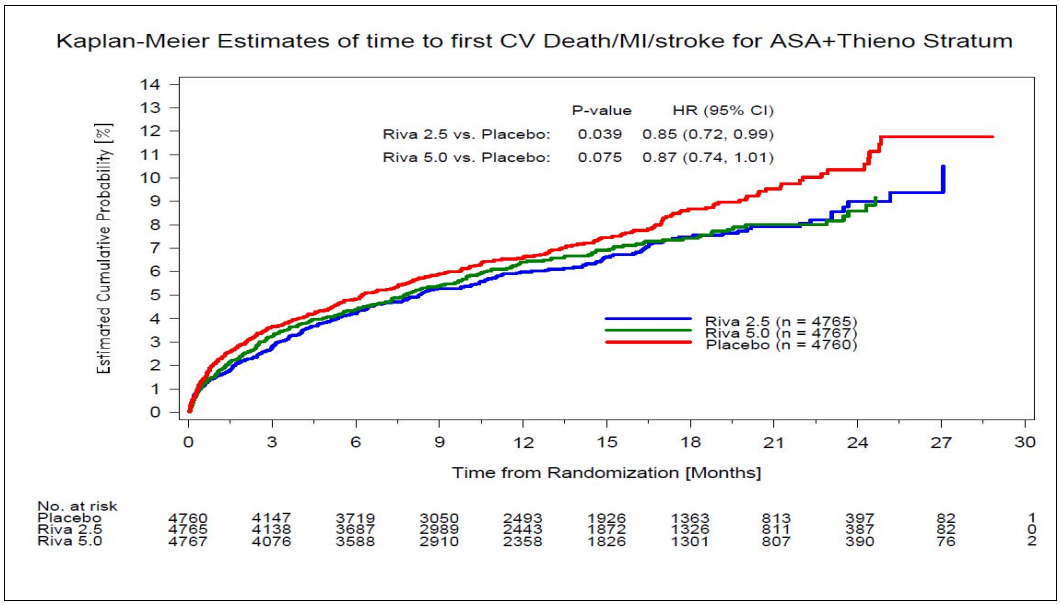
As we see from the forest plots of Figure 4, for Stratum 2, there is not much difference between each of above analysis sets in primary efficacy endpoint. However, we can see that if sponsor had used ITT, then all the findings will become much more significant. Most importantly, the efficacy finding of Rivaroxaban 5.0 mg would have achieved the statistical significance at 0.05 level. Figure 5 and Figure 6 captured the Kaplan-Meier curves of the three treatment groups in All Strata and Stratum 2, respectively. They showed clear separations between the two dosage groups with placebo around 18 months into the randomization and maintained the separation throughout the remainder of the trial.

Figure 5 Kaplan-Meier Estimates of the Primary Efficacy Endpoint in All Strata: mITT(Exc Sites 091001, 091019 and 091026)



[Source: Reviewer's Results]

Figure 6 Kaplan-Meier Estimates of the Primary Efficacy Endpoint in Stratum 2: mITT(Exc Sites 091001, 091019 and 091026)

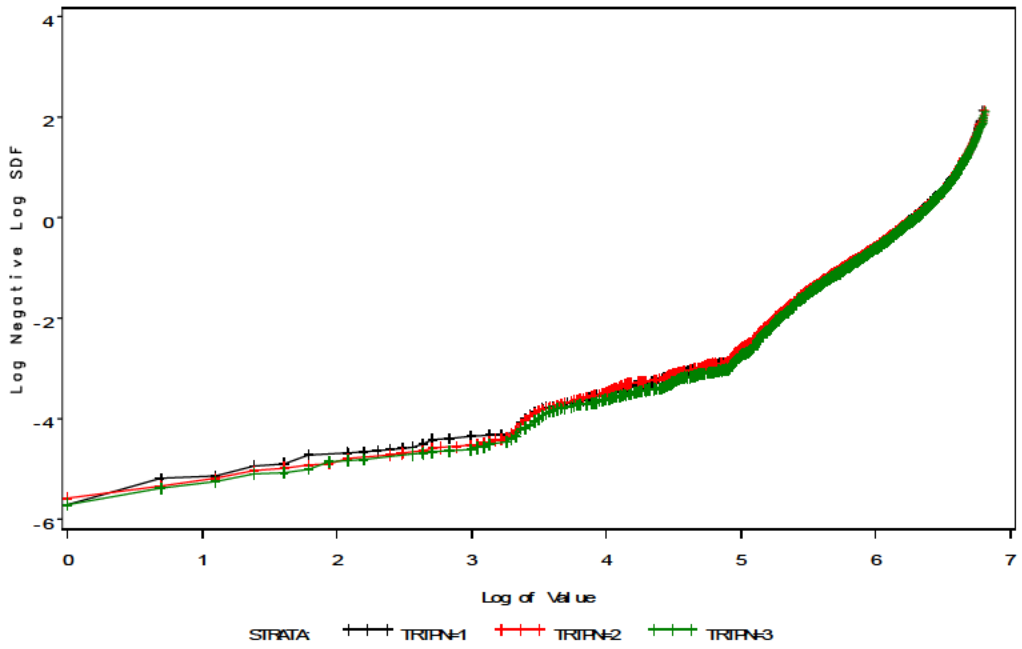


[Source: Reviewer's Results]

Validation of the Proportional Hazard Assumption

The basic Cox Model assumes that the hazard functions for two different levels of a covariate are proportional for all values of time, t. For example, if men have twice the risk of heart attack compared to women at age 50, they also have twice the risk of heart attack at age 60, or any other age. The underlying risk of heart attack as a function of age can have any form. Therefore, the validity of the Cox regression findings hinges on the proportional hazard assumption. A simple and common approach to check this assumption is through the plot of log(-log(S(t))) vs. log(t). However, the interpretation of the plot is subjective. In general, we feel comfortable with the assumption unless a distinct pattern of non-parallelism (e.g. crossing) is seen. However, we can not draw any informative conclusion based on Figure 7 about the PH assumption. This inconclusiveness may be due to the reason the event rates among three treatment groups are extremely close to one another, see Table 3.

Figure 7 Log(-Log(Survival)) vs. Log(Time) Plot



To further explore the validity of this assumption, I introduced treatment and time interaction into the model. Table 4 indicated that the both interaction terms did not achieve statistical significance at the 0.05 level with a large p-value. It is reasonable to assume that there is support for the proportional hazard assumption.

Table 4 Numerical Test of Proportional Hazard Assumption

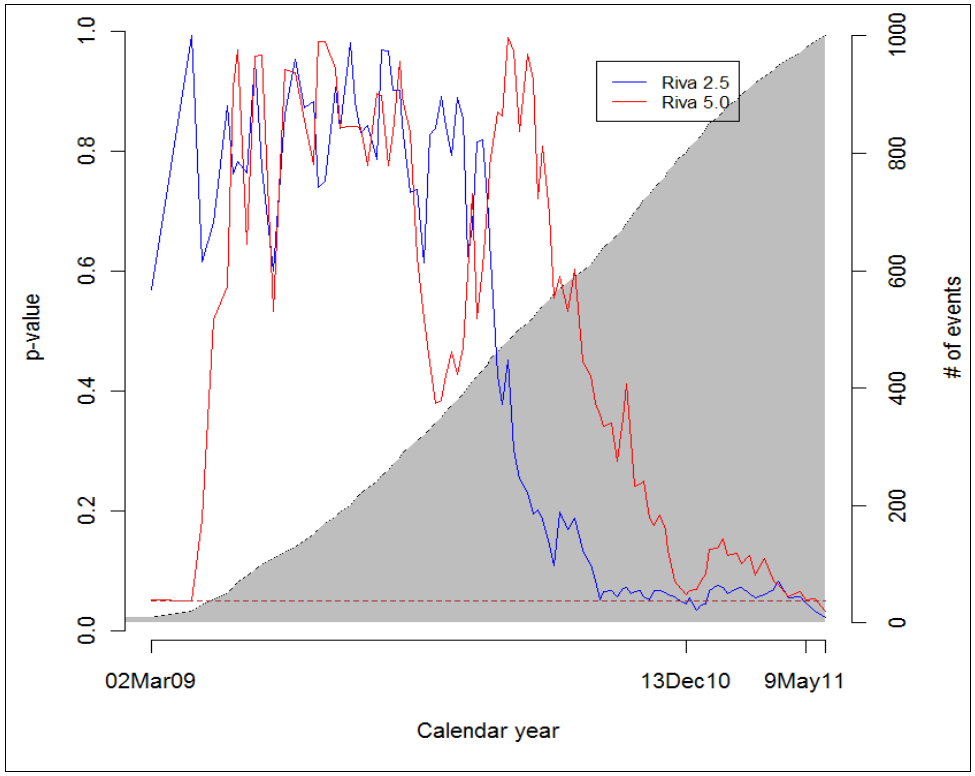
Linear Hypotheses Testing Results			
Label	**Wald Chi-Square**	**DF**	**Pr > ChiSq**
Riva 5.0 mg proportionality_test	0.2713	1	0.6025
Linear Hypotheses Testing Results			
Label	**Wald Chi-Square**	**DF**	**Pr > ChiSq**
Riva 2.5 mg proportionality_test	1.0959	1	0.2952

[Source: Reviewer's Results]

Analysis on the Impact of Different End of Trial Dates

In All Strata, both Rivaroxaban dose groups achieved statistical significance difference with placebo no matter which analysis sets are used and whether to exclude those 3 Indian sites or not. It would be very useful to find out how early those findings were established during the course of the trial. Figure 8 shows the p-values for the primary endpoint as a function of calendar time of the study. In this figure, I changed the event (censor) status and time to event information as if the current calendar time is assumed be the end of trial date starting from 03/02/2009 to 06/03/2011 (actual trial ending date). The original Cox regression analysis with treatment in the model was performed for each day. The red curve is the p-value of Riva 5.0mg, and the blue curve is the p-value Riva 2.5 mg. Base on the figure, we can see that 12/13/2010 was first time Riva 2.5 mg crossed below 0.05. 05/09/2011 was last time the p-value of Riva 2.5 mg stayed above 0.05. However, Riva 5.0 mg only achieved the statistical significance a few days before the end of trial. The red dash horizontal line is the statistical significance level of 0.05. These findings are based on mITT analysis set excluded three sites in All Strata.

Figure 8 Cox Model P-values of the primary composite endpoint across trial calendar date (All Strata MITT Exclude 3 sites)



[Source: Reviewer's Results]

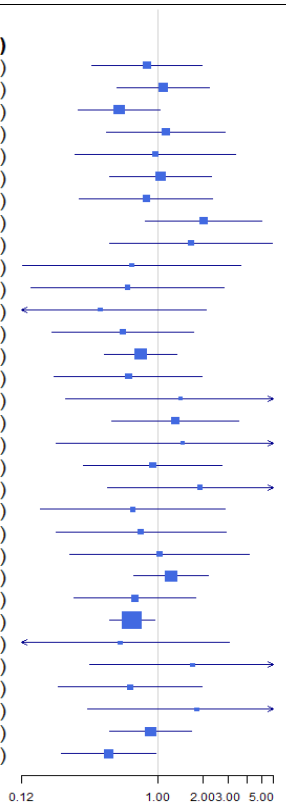
Analysis on the Impact of Individual Country

ATLAS was conducted at 766 centers in 44 countries. The original Cox model is applied for each country in the mITT analysis set in All Strata which excluded three Indian sites. Among these countries, Rivaroxaban 2.5 mg was numerically superior to placebo in many countries (see Figure 9). Russian is the largest enrolling nation and had most of primary efficacy events, which also demonstrated statistically superior finding. Rivaroxaban 2.5 mg is also shown to be effective in reducing the incidences of CV deaths, MI or Stroke in Unite States. (HR=0.465 and the upper bound of 95% CI is 0.969, which is below 1.0)

Figure 10 display the results of the subgroup analysis comparing Rivaroxaban 5.0 mg b.i.d with placebo for the primary efficacy endpoint in the mITT analysis set in All Strata. Both Russia and Unites States, again, exhibited numerically but not statistically superior findings in reducing the incidences of CV deaths, MI or Stroke.

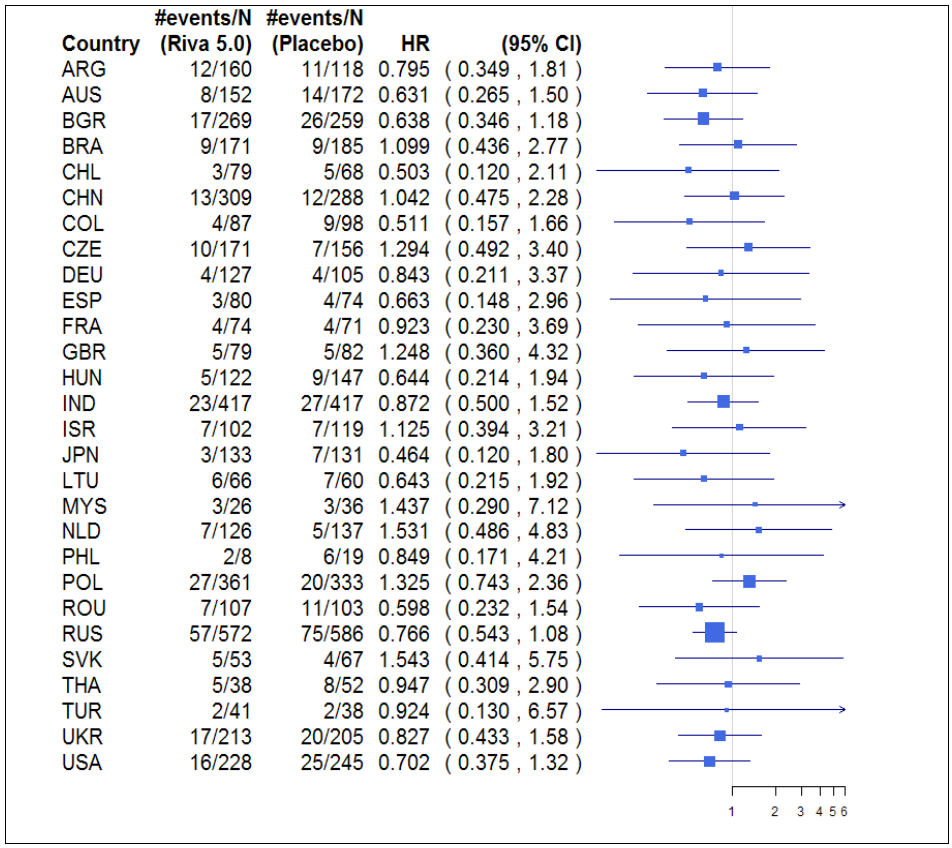
Figure 9 The Forest Plots of Hazard ratio and 95% CI for Primary Endpoint comparing Riva 2.5 mg to Placebo by countries

Country	#events/N (Riva 2.5)	#events/N (Placebo)	HR	(95% CI)
ARG	10/126	11/118	0.84	(0.3568 , 1.979)
AUS	16/186	14/172	1.085	(0.5297 , 2.224)
BGR	15/264	26/259	0.546	(0.2893 , 1.031)
BRA	9/173	9/185	1.133	(0.4491 , 2.857)
CHL	5/66	5/68	0.962	(0.2777 , 3.331)
CHN	13/304	12/288	1.042	(0.4754 , 2.284)
COL	6/84	9/98	0.834	(0.2957 , 2.352)
CZE	14/158	7/156	2.027	(0.8179 , 5.024)
DEU	6/100	4/105	1.668	(0.4698 , 5.920)
EGY	2/48	4/64	0.662	(0.1212 , 3.617)
ESP	3/76	4/74	0.622	(0.1385 , 2.796)
GBR	2/93	5/82	0.406	(0.0783 , 2.103)
HUN	5/143	9/147	0.579	(0.1938 , 1.733)
IND	22/451	27/417	0.762	(0.4338 , 1.338)
ISR	5/132	7/119	0.632	(0.2005 , 1.992)
ITA	3/78	2/79	1.416	(0.2363 , 8.481)
JPN	9/136	7/131	1.312	(0.4881 , 3.524)
KOR	2/41	2/57	1.471	(0.2072 , 10.446)
LTU	7/51	7/60	0.922	(0.3161 , 2.692)
MYS	5/35	3/36	1.914	(0.4569 , 8.019)
NLD	3/114	5/137	0.677	(0.1615 , 2.836)
NZL	4/31	5/28	0.769	(0.2061 , 2.866)
PHL	3/11	6/19	1.024	(0.2554 , 4.106)
POL	26/368	20/333	1.23	(0.6864 , 2.203)
ROU	7/94	11/103	0.7	(0.2715 , 1.807)
RUS	53/598	75/586	0.67	(0.4714 , 0.953)
SVK	2/58	4/67	0.553	(0.1013 , 3.023)
SWE	3/41	3/59	1.717	(0.3457 , 8.523)
THA	5/50	8/52	0.649	(0.2124 , 1.986)
TUR	4/40	2/38	1.837	(0.3364 , 10.031)
UKR	18/211	20/205	0.898	(0.4751 , 1.698)
USA	10/211	25/245	0.465	(0.2233 , 0.969)



[Source: Reviewer's Results]

Figure 10 The Forest Plots of Hazard ratio and 95% CI for Primary Endpoint comparing Riva 5.0 mg to Placebo by countries



[Source: Reviewer's Results]

Analyses of Individual Components of the Composite Efficacy Endpoints

The Cardiovascular Death, MI and Stroke were the components of the primary efficacy endpoint. Table 5 summarized the effects of Rivaroxaban compared with placebo on each of these three components in the mITT analysis set for both All Strata and Stratum 2. These components are analyzed in two ways:

1. Analysis of individual components which contributed to the makeup of primary composite, see Decomposition of the first primary event of Table 5. Due to the severe competing risk issue, no formal statistical testing results (95% CIs and p-values) are present for this exploratory analysis.
2. Analysis of first occurrence of individual component endpoint, see Decomposition for any occurrence of individual components of Table 5.

Table 5 Effect of Rivaroxaban Compared with Placebo on the individual components of Primary Efficacy Endpoints

Stratum	Rivaroxaban									
Parameter	**2.5 mg BID**	**5.0 mg BID**	**Combined**	**Placebo**	**2.5 mg BID vs. Placebo HR (95% CI)**	**P-value**	**5.0 mg BID vs. Placebo HR (95% CI)**	**P-value**	**Combined vs. Placebo HR (95% CI)**	**P-value**
1. Decomposition of the first primary event *										
All Strata	**N= 5114**	**N=5115**	**N=10229**	**N=5113**						
CV Death	73 (1.4%)	96 (1.9%)	169 (1.7%)	112 (2.2%)	0.66	-	0.87	-	0.76	-
MI	199 (3.9%)	167 (3.3%)	366 (3.6%)	227 (4.4%)	0.88	-	0.75	-	0.82	-
Stroke	41 (0.8%)	50 (1.0%)	91 (0.9%)	37 (0.7%)	1.12	-	1.38	-	1.25	-
ASA + Thieno	**N=4765**	**N=4767**	**N=9532**	**N=4760**						
CV Death	64 (1.3%)	89 (1.9%)	153 (1.6%)	103 (2.2%)	0.63	-	0.88	-	0.75	-
MI	183 (3.9%)	158 (3.3%)	341 (3.6%)	205 (4.3%)	0.90	-	0.79	-	0.84	-
Stroke	39 (0.8%)	42 (0.9%)	81 (0.7%)	32 (0.70)	1.23	-	1.34	-	1.29	-
2. Decomposition for any occurrence of individual components										
All Strata	**N= 5114**	**N=5115**	**N=10229**	**N=5113**						
CV Death	94 (1.8%)	132 (2.6%)	226 (2.2%)	143 (2.8%)	0.66 (0.51, 0.86)	0.002	0.94 (0.75, 1.20)	0.633	0.80 (0.65,0.99)	0.038
MI	205 (4.0%)	179 (3.5%)	384 (3.8%)	229 (4.5%)	0.90 (0.75, 1.09)	0.270	0.79 (0.65, 0.97)	0.020	0.85 (0.72, 1.00)	0.047
Stroke	46 (0.9%)	54 (1.1%)	100 (1.0%)	41 (0.8%)	1.13 (0.74, 1.73)	0.562	1.34 (0.90, 2.02)	0.151	1.24 (0.86, 1.78)	0.246
ASA + Thieno	**N=4765**	**N=4767**	**N=9532**	**N=4760**						
CV Death	82 (1.7%)	123 (2.6%)	205 (2.2%)	133 (2.8%)	0.62 (0.47, 0.82)	0.001	0.95 (0.74, 1.21)	0.669	0.78 (0.63,0.98)	0.028
MI	189 (4.0%)	169 (3.5%)	358 (3.8%)	207 (4.4%)	0.92 (0.76, 1.12)	0.402	0.83 (0.68, 1.02)	0.078	0.88 (0.74, 1.04)	0.131
Stroke	44 (0.9%)	46 (1.0%)	90 (0.71%)	34 (0.70)	1.31 (0.84, 2.05)	0.238	1.39 (0.89, 2.16)	0.144	1.35 (0.91, 2.00)	0.137

[Source: Reviewer's Results]

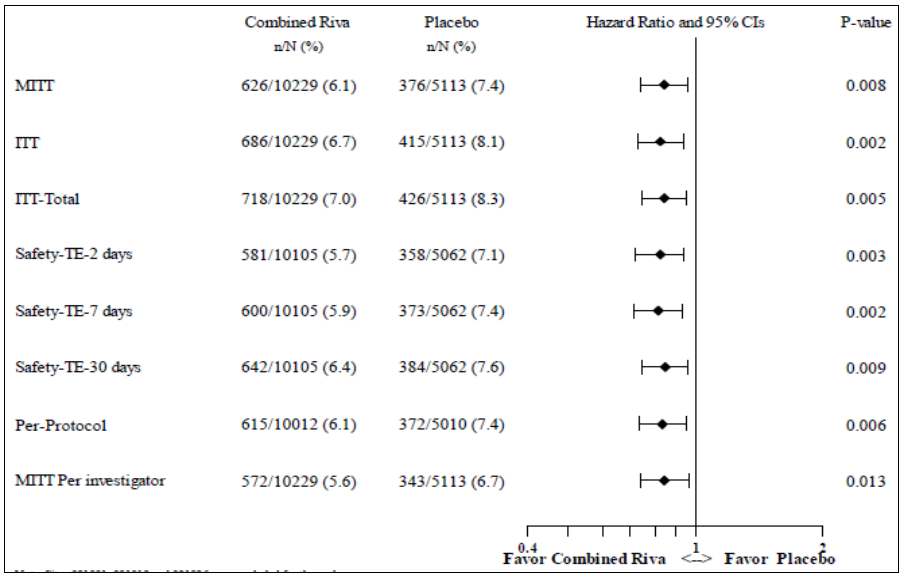
* no CIs and p-values are calculated because of severe competing risk problem

In both All Strata and Stratum 2, both analyses showed the combined and individual Rivaroxaban doses all have numerical benefit compared with placebo in reducing CV death and MI. The point estimates of HRs are all less than 1.0. However, both analyses showed that all Rivaroxaban groups had numerically more strokes (inferior) than the placebo group in both All Strata and Stratum 2.

Sensitivity Analyses

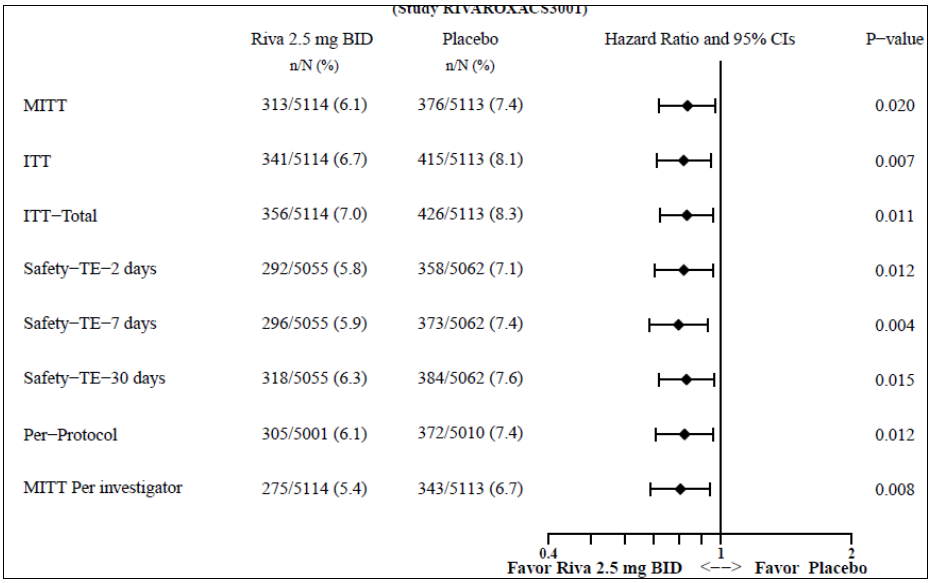
Figure 11 to Figure 13 summarized the results of the sensitivity analyses of the primary efficacy endpoint for the combined and each Rivaroxaban dose compared with placebo in All Strata. The primary efficacy endpoint was analyzed, using the same methods as those used for the primary efficacy analysis in the mITT analysis set, in the ITT, ITT-Total and Treatment-Emergent Safety analysis sets with three Indian sites removed. The results of the sensitivity analyses were generally consistent with the results of the primary efficacy analysis in showing significant results favoring Rivaroxaban 2.5 mg. Similar findings were also observed in the forest plots of sensitivity analyses for the Rivaroxaban 5.0 mg.

Figure 11 Effect of Combined Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (All Strata Excluding Sites 091001, 091019, 091026)



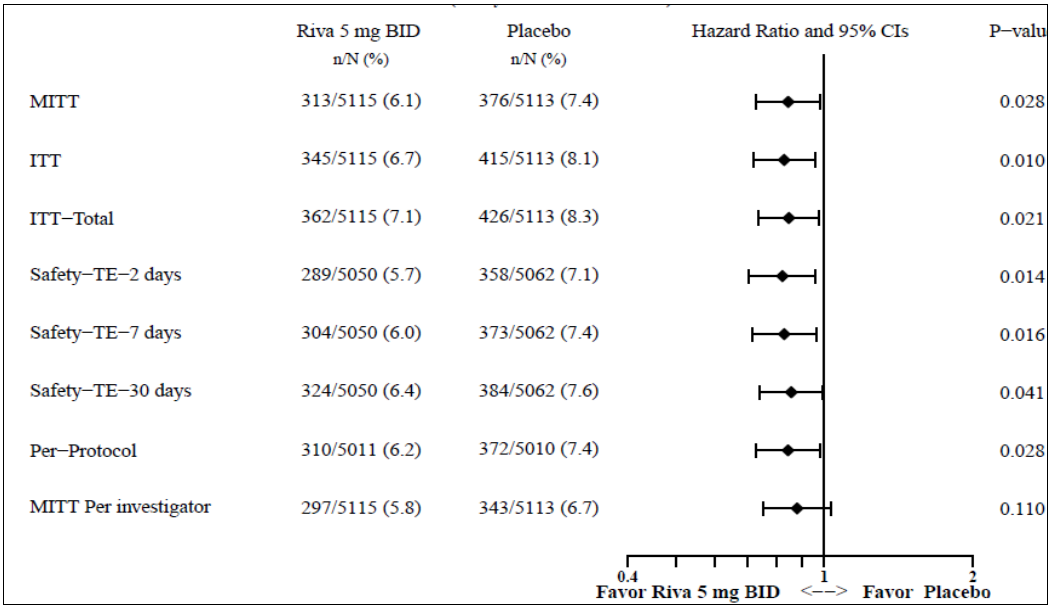
[Source: Sponsor's Study Report page146, verified by the reviewer]

Figure 12 Effect of Rivaroxaban 2.5 mg Compared with Placebo on the Primary Efficacy Endpoint (All Strata Excluding Sites 091001, 091019, 091026)



[Source: Sponsor's Study Report page1483]

Figure 13 Effect of Rivaroxaban 5.0 mg Compared with Placebo on the Primary Efficacy Endpoint (All Strata Excluding Sites 091001, 091019, 091026)



[Source: Sponsor's Study Report page1484]

Secondary Efficacy Analysis

As pre-specified in the hierarchical testing strategy outlined in the SAP, the findings of significance for the primary efficacy endpoint meant that further analyses for the secondary efficacy endpoints could be performed. There was no agreement on this testing strategy throughout entire ACS program. This reviewer does not agree with the allowance of the formal testing of the secondary endpoints on the 2.5 mg b.i.d. and 5.0 mg b.i.d. Hence, the descriptive results of the four secondary endpoints are listed in Table 6 for both All Strata and Stratum 2.

Table 6 Effect of Rivaroxaban Compared with Placebo on the Secondary Efficacy Endpoints and Components as Adjudicated by the CEC: mITT (Excluding Sites 091001, 091019 and 091026)

Stratum	**2.5 mg BID**	**5.0 mg BID**	**Placebo**	**2.5 mg vs. Placebo**	**5.0 mg vs. Placebo**	**Combined vs. Placebo**
All Strata	**(N=5114) n%**	**(N=5115) n%**	**(N=4760) n%**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Dth/MI/St	320 (6.3%)	321 (6.3%)	386 (7.5%)	0.83 (0.72, 0.97)	0.84 (0.73, 0.98)	0.84 (0.74, 0.95)
Net Clin. Outcome	361 (7.0%)	366 (7.2%)	391 (7.6%)	0.93 (0.81, 1.07)	0.95 (0.83, 1.10)	0.94 (0.83, 1.06)
CV Dth/MI/St/SRIR	437 (8.5%)	421 (8.2%)	481 (9.4%)	0.92 (0.80, 1.04)	0.89 (0.78, 1.01)	0.90 (0.81, 1.01)
CV Dth/MI/St/SRIH	372 (7.3%)	388 (7.6%)	447 (8.7%)	0.84 (0.73, 0.96)	0.88 (0.77, 1.01)	0.86 (0.76, 0.97)
ASA + Thieno	**(N=4765) n%**	**(N=4767) n%**	**(N=4760) n%**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Dth/MI/St	292 (6.1%)	297 (6.2%)	350 (7.4%)	0.84 (0.72, 0.98)	0.87 (0.74, 1.01)	0.85 (0.75, 0.97)
Net Clin. Outcome	333 (7.0%)	341 (7.2%)	355 (7.5%)	0.95 (0.82, 1.10)	0.98 (0.85, 1.14)	0.96 (0.85, 1.10)
CV Dth/MI/St/SRIR	406 (8.5%)	393 (8.2%)	442 (9.3%)	0.93 (0.81, 1.06)	0.91 (0.79, 1.04)	0.92 (0.82, 1.03)
CV Dth/MI/St/SRIH	340 (7.1%)	358 (7.5%)	405 (8.5%)	0.85 (0.73, 0.98)	0.90 (0.78, 1.04)	0.87 (0.77, 0.99)

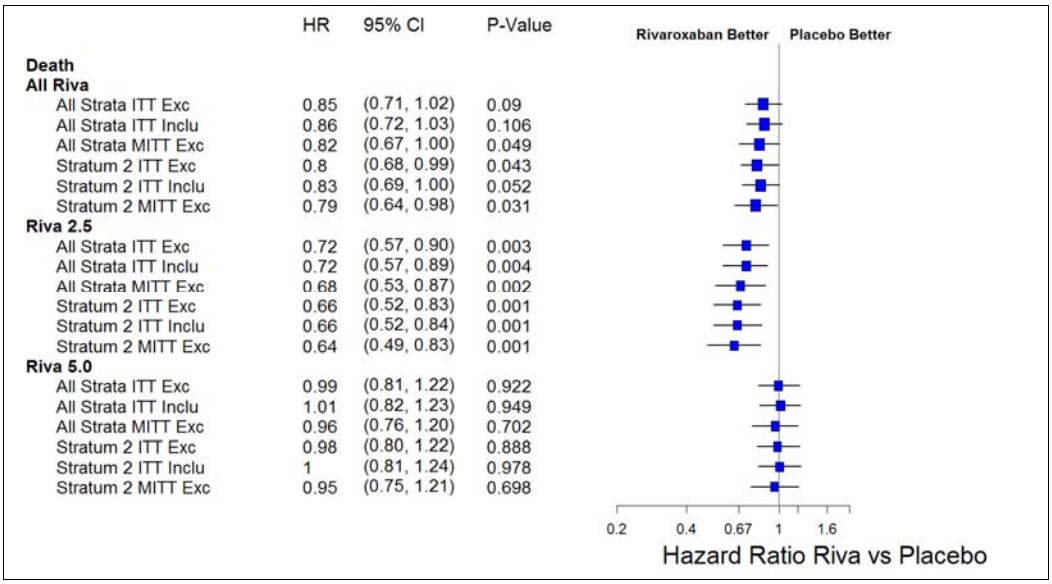
[Source: Reviewer's Results]

Analysis of All-cause Death

All-cause death was one of the components of Secondary Efficacy Endpoint 1 and the effect of Rivaroxaban compared with placebo on primary efficacy endpoint was also largely driven by the reduction of CV deaths, which made up over 92% (226 out of 245) of all-cause deaths. It would be worthwhile to explore the effect of Rivaroxaban on all-cause deaths. Based on the forest plots of Figure 14, we see that Rivaroxaban 2.5 mg b.i.d. was superior to placebo in reducing the occurrence of all-cause deaths no matter which analysis sets are used. However, the 5.0 mg b.i.d had little effect for the reduction of all-cause deaths. The most importantly, the benefit of the combined doses in reduction of all-cause deaths is neither strong nor robust.

The reason is that the 5.0 mg b.i.d. neutralized the findings of 2.5 mg b.i.d. dose. The board line effectiveness finding of All Strata mITT (excluded 3 Indian sites) analysis set went away in the ITT analysis sets (Include and exclude 3 Indian Sites). In Stratum 2, the effect of the combined doses heavily depended on the inclusion/ exclusion of those 3 Indian sites.

Figure 14 Mortality in ATLAS (All Cause Death)



[Source: Reviewer's Results]

3.3 Evaluation of Safety

Safety is not evaluated in this review. Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

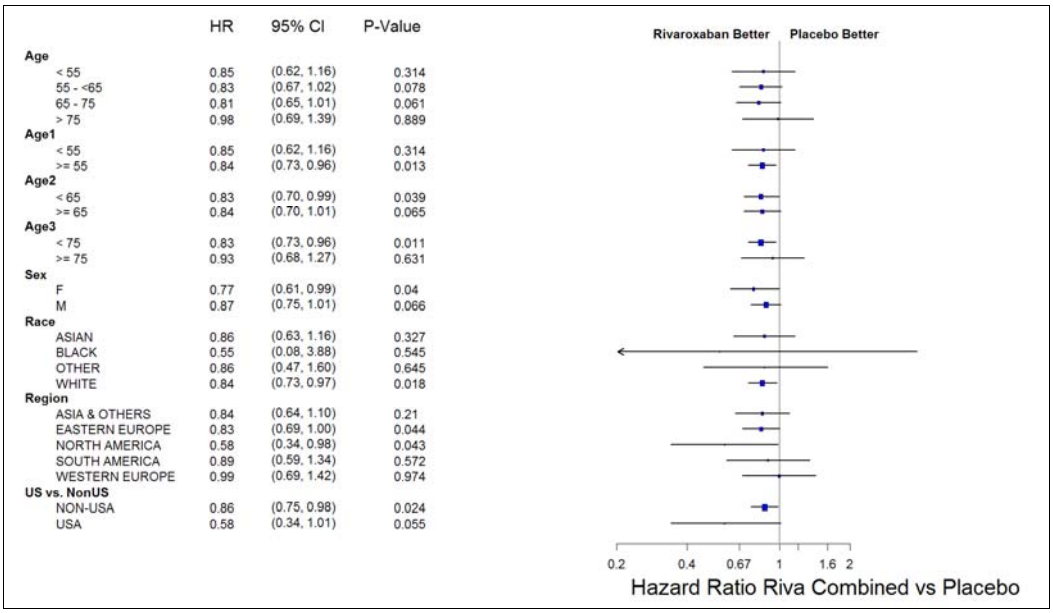
Various subgroup analyses were performed to explore whether the efficacy of Apixaban was markedly different among different subgroups compared to that observed in the primary efficacy results.

4.1 Age, Sex, Race and Geographical Region

Figure 15 to Figure 17 display the primary efficacy results of the subgroup analyses for different Age, Sex, Race, Geographical regions. They compared the combined Rivaroxaban groups, as well as 2.5 mf b.i.d. and 5 mg b.i.d. groups individually with placebo in the mITT analysis set in All Strata. A favorable HR for Rivaroxaban compared with placebo was observed across the majority of the subcategories of these three subgroups for both dose groups.

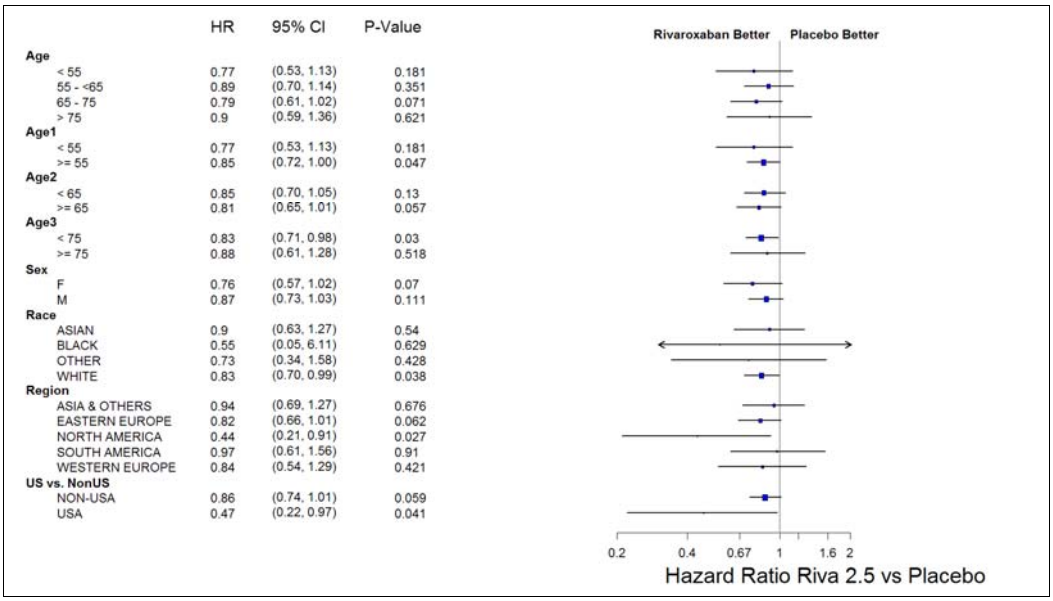
The benefits of Rivaroxaban within United States were demonstrated and exceed the Non US nations' results. In fact, the statistical significances in reducing the incidence of primary efficacy endpoint were observed for combined dose and 2.5 mg b.i.d.

Figure 15 Hazard Ratios of the Primary Efficacy Endpoint by Age, Sex, and Race for Combined Rivaroxaban Compared With Placebo in All Strata



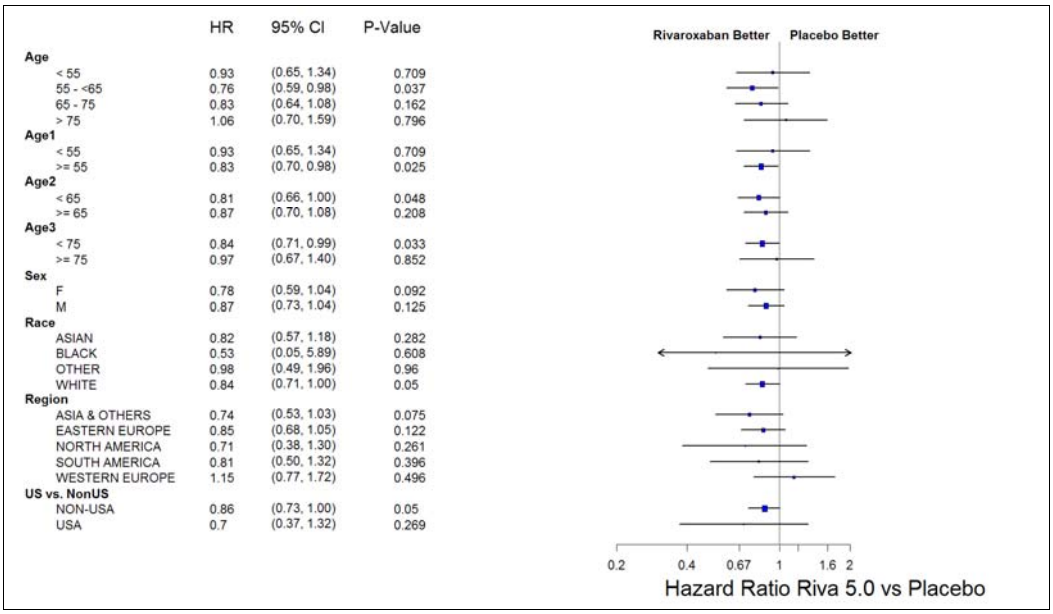
[Source: Reviewer's Results]

Figure 16 Hazard Ratios of the Primary Efficacy Endpoint by Age, Sex, and Race for Rivaroxaban 2.5 mg Compared With Placebo in All Strata



[Source: Reviewer's Results]

Figure 17 Hazard Ratios of the Primary Efficacy Endpoint by Age, Sex, and Race for Rivaroxaban 5.0 mg Compared With Placebo in Stratum 2

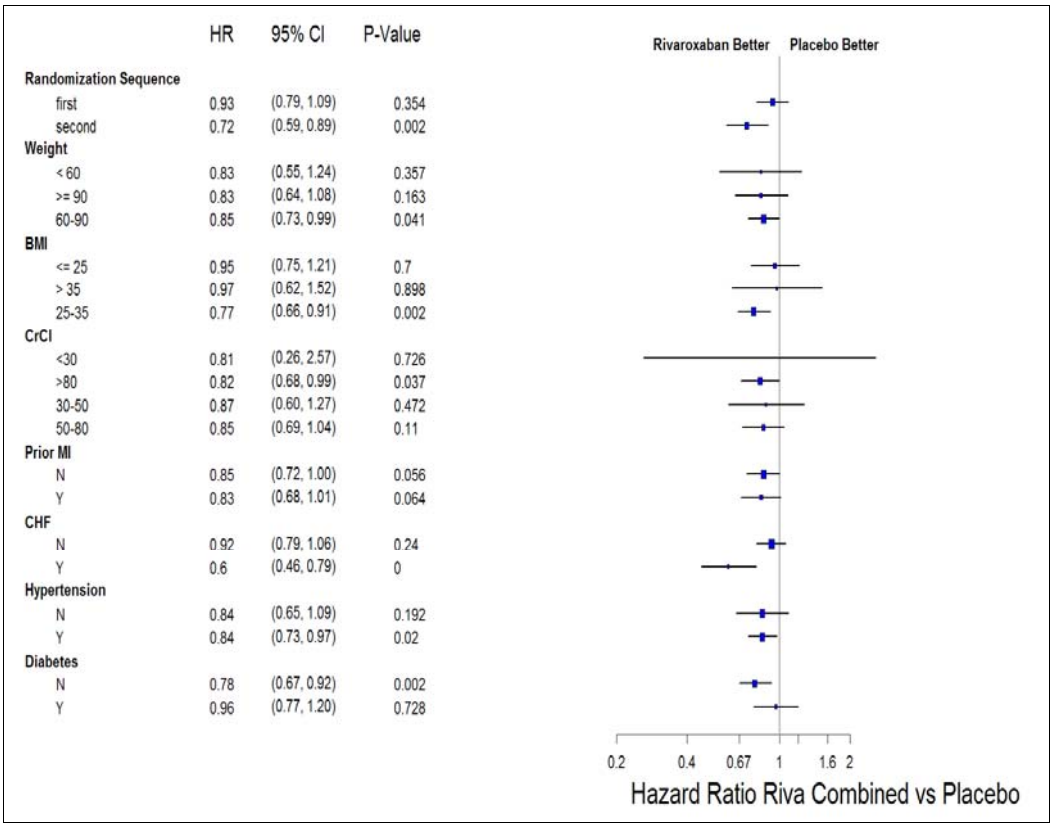


[Source: Reviewer's Results]

4.2 Other Subgroup Populations

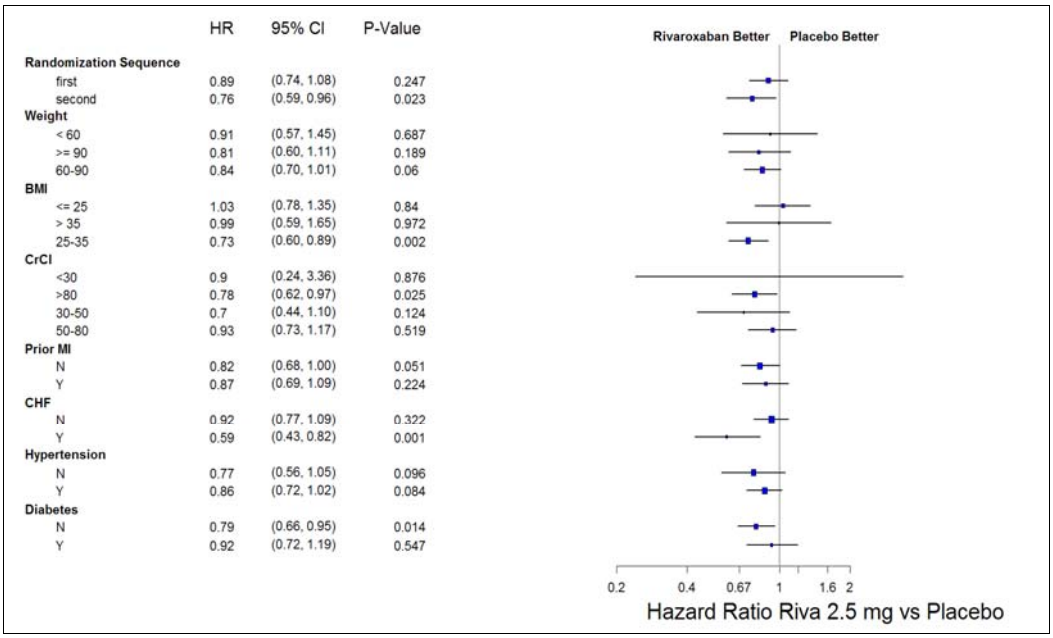
The primary efficacy results based on other additional subgroups such as Baseline weight, BMI, CrCL, Prior MI, etc. are explored. These results are displayed for Combined Rivaroxaban, as well as 2.5 mg b.i.d. and 5.0 mg b.i.d., respectively, in Figure 18 to Figure 20.

Figure 18 Hazard Ratios and Rates of the Primary Efficacy Endpoint by Other Subgroup for Combined Rivaroxaban Compared With Placebo in All Strata



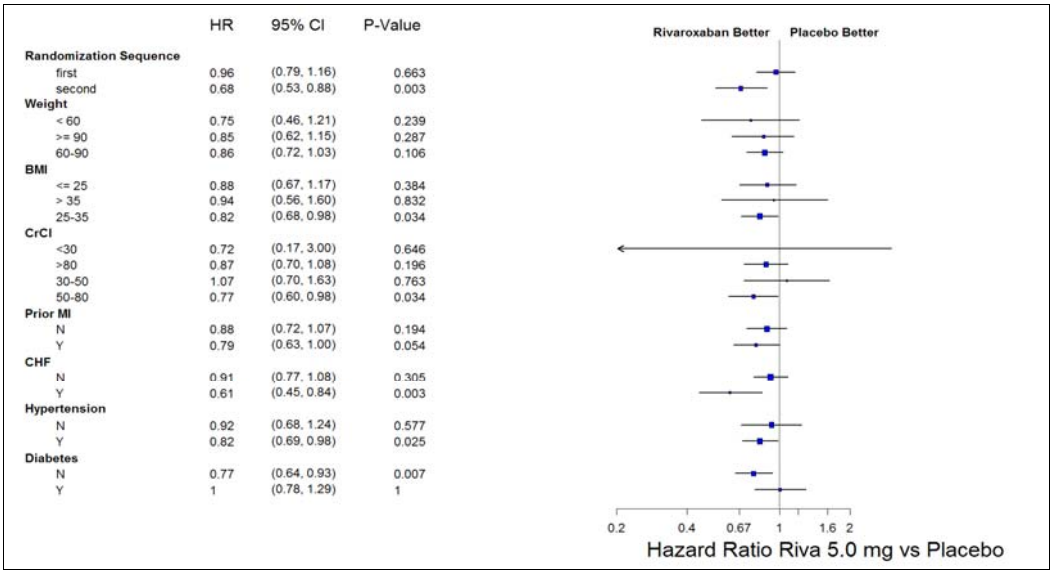
[Source: Reviewer's Results]

Figure 19 Hazard Ratios and Rates of the Primary Efficacy Endpoint by Other Subgroup for Rivaroxaban 2.5 mg Compared With Placebo in All Strata



[Source: Reviewer's Results]

Figure 20 Hazard Ratios and Rates of the Primary Efficacy Endpoint by Other Subgroup for Rivaroxaban 5.0 mg Compared With Placebo in All Strata



[Source: Reviewer's Results]

In general, the more favorable HR for Rivaroxaban compared with placebo was observed across the most of subgroups for both dose groups. However, one of the interesting finding we observed if that most of Rivaroxaban effect are demonstrated in the second half of the trial. There are no differences between Rivaroxaban and Placebo within the subjects recruited first.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary efficacy objective of this study was to determine whether Rivaroxaban reduces the risk of the composite of CV death, MI, or stroke in subjects with a recent ACS compared with placebo in addition to standard care. In addition, the major secondary objectives were to determine whether Rivaroxaban reduces the risk of the secondary composite endpoints compared with placebo. As pre-specified in the SAP, 2 simultaneous evaluation strategies, based on data combined across both strata and on data for Stratum 2 only, were used for the efficacy analyses. Further, both for the analyses of the combined strata and for the analyses of Stratum 2, hierarchical testing in sequential order was performed for the analyses of the primary and secondary efficacy endpoints. There are several places that the multiplicity issues of the inflation of familywise error rate could occur:

- Two identical strategies are tested at 0.05 level simultaneously, the agency had informed the sponsor that both strategies have to be successful in order to claim the overall success of the entire program. However, the sponsor had never responded the agency's statistical advice letter.
- Within each strategy, the secondary efficacy endpoints are to be tested sequentially at 0.05 level for either of two doses if combined dose and the corresponding dose won on its' primary efficacy endpoint at 0.05 level. The agency, again, had informed the sponsor that this strategy will inflate the overall type I error even if there is only one testing strategy.
- Lastly, agency had encouraged sponsor not to spend alpha on the proposed secondary endpoints, because they are similar to the primary endpoint. The likelihood of getting a claim based on the proposed secondary endpoints is low.

In All Strata, the combined Rivaroxaban groups were superior to placebo, in addition to standard care, in reducing the occurrence of the primary composite efficacy endpoint (i.e., CV death, MI or stroke) in subjects with a recent ACS in the mITT analysis set (HR 0.84; 95% CI 0.74-0.96; P=0.008). Further, the 2.5 mg b.i.d. and 5 mg b.i.d. groups each achieved superiority to placebo in the primary efficacy endpoint. In Stratum 2, the combined Rivaroxaban doses were superior to placebo in reducing the occurrence of the primary efficacy endpoint (HR 0.86; 95% CI 0.75, 0.98; P=0.024). However, only the 2.5 mg b.i.d. Rivaroxaban group achieved statistical significance for the primary efficacy endpoint. This review also listed the four secondary efficacy endpoints results as exploratory findings, and only the descriptive results are provided in Table 6.

In order to resolve the simultaneous testing strategies, this review had treated the Stratum 2 as a subgroup analysis even though All Strata is completely driven by the Stratum 2 (consisted over 90% of trial subjects).

In addition, there were disagreements between the agency and sponsor on whether mITT or ITT analysis sets should be the primary efficacy analysis set. Agency had always recommended ITT analysis set should be the primary efficacy analysis dataset. Fortunately, the primary efficacy results based on ITT closely mirrored and improved the results of mITT dataset. Lastly, sponsor made the late change to the SAP by removing three Indian sites due to trial misconducts. However, the Inclusion/Exclusion of three sites did not affect the overall trial results greatly.

5.2 Conclusions and Recommendations

The following conclusions can be drawn from the ATLAS ACS 2 TIMI 51 trial:

- In All Strata, including the subjects with the use of ASA and a thienopyridine plus ASA, Rivaroxaban was effective in reducing the occurrence of the composite primary endpoint of cardiovascular death, myocardial infarction or stroke compared with placebo in subjects with a recent ACS. The combined Rivaroxaban dose, the 2.5 mg b.i.d. and the 5 mg b.i.d. were effective in reducing the occurrence of the primary efficacy endpoint.
- In Stratum 2, including the subjects only with the use a thienopyridine plus ASA, Rivaroxaban was effective in reducing the occurrence of the composite primary endpoint of cardiovascular death, myocardial infarction or stroke compared with placebo in subjects with a recent ACS. The combined Rivaroxaban doses and the 2.5 mg b.i.d. were effective in reducing the occurrence of the primary efficacy endpoint.
- The above findings were largely driven by the reduction of CV deaths particularly in the 2.5 mg b.i.d. dose group. The 2.5 mg b.i.d. dose of Rivaroxaban was also nominally statistically significant in reducing the incidence of all cause deaths in All Strata and Stratum 2. However, the 5.0 mg b.i.d was not shown effective and appeared to have little effect for the reduction of all cause deaths. Furthermore, the reduction of all cause deaths was not statistically robust for the combined doses. The board line effectiveness finding depends on which analysis sets are used and whether 3 Indian sites to be excluded from the analyses.

CHECK LIST

Number of Pivotal Studies: 1

Trial Specification

Specify for each trial: ATLAS

Protocol Number (s): RIVAROXACS3001
Protocol Title (optional): The ATLAS ACS 2 TIMI 51 Trial (The Second Trial of Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome)
Phase: 3
Control: Placebo Control
Blinding: Double-Blind
Number of Centers: 766
Region(s) (Country): 44 countries
Duration: Event-driven trial, initiated on Nov 26, 2008 and completed on Sept 19, 2011
Treatment Arms: Rivaroxaban
Treatment Schedule: 2.5 mg b.i.d. and (5.0 mg b.i.d.
Randomization: Yes
Ratio: 1:1:1
Method of Randomization: stratification
If stratified, then the Stratification Factors: Thienopyridine use
Primary Endpoint: the first occurrence of the composite of CV death, MI, or stroke
Primary Analysis Population: mITT
Statistical Design: Superiority
Adaptive Design: No
Primary Statistical Methodology: Cox proportional hazard model
Interim Analysis: Yes
If yes:
No. of Times: 1
Method: Cox model
α Adjustment: Yes
α Spending Function: Haybittle-Peto
DSMB: Yes
Sample Size: 983 primary efficacy endpoint events (15,500 randomized)
Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes
Statistic = log-rank
Power= 96%
Δ= HR=0.775
α = 0.05

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation: Several sensitivity analyses are planned
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No
- Were the **Covariates** pre-specified in the protocol? No
- Did the Applicant perform **Sensitivity Analyses**? Yes
- How were the **Missing Data** handled? Subjects were censored when lost to follow up or 2 days after last study dose administered. Censoring was assumed non-informative in the log-rank test.
- Was there a **Multiplicity** involved? Yes

  If yes,

  Multiple Arms (Yes/No)? Yes

  Multiple Endpoints (Yes/No)? Yes

  Which method was used to control for type I error? Endpoints were tested sequentially in a pre-specified order.
- **Multiple Secondary Endpoints**: Are they being included in the label? If yes, method to control for type 1 error. Yes. Sequential testing

Were Subgroup Analyses Performed (Yes/No)? Yes

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No
- Overall, was the study positive (Yes/No)? Yes

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEVE G BAI
04/20/2012

HSIEN MING J HUNG
04/20/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 26, 2012

From: Thomas A. Marciniak, M.D.
Medical Team Leader

Subject: Data quality in the ATLAS ACS trial of rivaroxaban, NDA 202-439

To: Advisory Committee Members

This memo is a supplement to the primary reviews and addresses data quality issues in ATLAS. While Janssen Pharmaceuticals (JNJ) reports favorable statistical results for the primary endpoint as well as for all cause mortality, the validity of the statistical results depends upon the data being accurate and complete. I review the data that suggest that the data quality may not support the favorable statistical results.

Incomplete Follow-up

I show in Table 1 the patient status at the end of ATLAS per JNJ.

Table 1: Sponsor's Patient Status* at the End of ATLAS

	placebo	2.5	5
complete	85%	85%	84%
death	4%	3%	4%
good f/u	89%	88%	87%
consent withdrawn	8%	9%	9%
lost	0.3%	0.2%	0.3%
other	3%	3%	4%
bad f/u	11%	12%	13%

*TRLSTAT (Status at End of Study) in ADSL.XPT

COMMENT: Even by JNJ's assessment the percentage of patients with incomplete follow-up is high, averaging 12%. This percentage is far higher than the differences between the placebo and rivaroxaban arms in endpoint rates, which typically are about 1% to 1.5%. The difference between placebo and rivaroxaban for bad follow-up rates matches these differences in endpoint rates. By JNJ's patient status statistics there appears to be plenty of opportunity for incomplete data to obscure or magnify any differences in endpoints.

Missing Vital Status

Table 1 does not include follow-up for vital status only. JNJ reports trying to obtain vital status at the end of the study for all patients who did not withdraw consent for follow-up. However, JNJ was able to obtain vital status on a small minority of patients who withdrew consent as shown in Table 2.

Table 2: Sponsor's Patient Vital Status at the End of ATLAS

	placebo	2.5	5
consent withdrawn	8%	9%	9%
confirmed alive	1%	1%	1%
consent withdrawn – vital status unknown	7%	8%	7%
lost	0.3%	0.2%	0.3%
vital status unknown	7%	8%	8%
other	3%	3%	4%
vital status unclear	10%	11%	11%

Source: TRLSTAT and Table 10 from ATLAS Clinical Study Report

COMMENT: The rates of patients with unknown vital status greatly exceed the reported differences in mortality rates. We cannot have confidence that the claimed mortality benefits are real.

Uncounted Deaths

Another issue is whether the JNJ statistics are accurate and unbiased. In reviewing case report forms (CRFs) for patients who discontinued early I chanced upon one patient whom the site reported to have died but the death report was deleted. I queried JNJ about this patient and JNJ responded on 16 February 2012 with this answer:

> *1. Subject [redacted] had a date of death of* (b) (6) *entered on 17Jan11 but a query noted the date as beyond the trial range. No death is counted.*
>
> *a. Please explain.*
>
> **RESPONSE**
>
> a. Subject [redacted] withdrew their consent and had their end of study visit on August 30, 2010. The investigative site subsequently recorded the subject died on (b) (6) Because the date of the death was after the subject withdrew consent, the site was queried to remove this information from the CRF and the death was not counted.

b. We presume the death was not counted because of withdrawal of consent. Please identify all patients who had an endpoint or death not counted because of withdrawal of consent.

RESPONSE

b. In review of data for efficacy endpoints no events were noted to have been deleted due to occurring after the subject withdrew consent with the exception of the death described above for subject [redacted].

Below please find a table with all potential safety endpoint events which were deleted because the subject had withdrawn their consent prior to the event.

Subject	Event Verbatim	Event Start Date	Date of Consent Withdrawal
[Redacted]	Nose bleeding	5Jan2011	29Dec2010
[Redacted]	Rectal loss of bleed	24Nov2009	19Nov2009

Note that JNJ responded that no other efficacy endpoint events were noted to have been deleted due to occurring after the subject withdrew consent. However, I subsequently identified two other patients who had deaths similarly not counted. I show some relevant facts for these cases in Table 3.

Table 3: Three Uncounted Deaths in ATLAS

dose	withdrew consent	died	sponsor's censored	sponsor's status
5	06/14/10	(b) (6)	08/30/10	alive
2.5	01/16/11	*	07/17/11	alive
5	12/23/09	(b) (6)	07/17/11	alive

*reported dead per phone contact with family 07/17/11

Note that all of these patients are rivaroxaban patients, JNJ counted all of them as alive for its analyses, and JNJ's censoring dates appear to have no relationship to the dates when consent was withdrawn or to the dates of death. I queried JNJ about all three of these patients and JNJ's response from 5 April 2012 regarding the second patient explains JNJ's approach to the censoring dates:

Subject [redacted] was confirmed as having died at the last phone follow-up on 17jul11. The prior regular phone contact was on 2jan11 with an unscheduled phone contact on 16jan11 with little information provided.
a. Why was more information on the unscheduled visit not sought?
b. Why was more information on the death not sought?
c. Why is this patient not reported as having died?
d. Why is the reference end date for this patient 17jul11?

RESPONSE
a. The subject withdrew their consent at this unscheduled visit (16 Jan 11).
b. Subject withdrew their consent and therefore further information could not be obtained per regulatory guidelines.
c. See response for b.
d. This was the last contact with the patient or their family.

JNJ counted the date of last phone contact with the family, at which the family reported that the patient had died, as the censoring date for this patient counted as alive despite the death report.

COMMENT: These three uncounted deaths may be the tip of the iceberg regarding problems with missing data. These deaths were deleted or not counted because they occurred after withdrawal of consent. We have no idea how many such deaths (and other endpoints) were deleted, not entered, or otherwise not counted among the 7% of patients who withdrew consent and have incomplete vital status in ATLAS. Also, JNJ's approach to censoring dates is inappropriate and overstates the completeness of follow-up in ATLAS and may overstate efficacy, as I address later. Finally, while three uncounted deaths may appear trivial, they do affect the interpretation of the primary analysis of mortality as I present later.

Poorly Documented Follow-up and Inappropriate Censoring
As the last example (box above) illustrates, the last follow-up and censoring dates in ATLAS were problematic. Another example of the inappropriate approaches is the following instruction from the statistical analysis plan:

If the subject remains as "Lost To Follow Up", the Visit Date for the End of Treatment & End of Trial Visits will be the date of the certified / courier letter sent to the subject.

Because the eCRFs did not capture the details of such letters, we do not know how many times follow-up is based on a certified letter—regardless of whether the patient or other party provided follow-up information in response to the letter. I did chance upon the following example from an end of trial eCRF:

1.	Did the subject complete the follow-up period?	No Reason for not completing: Other Specify: Pt did not return for follow up visit. Calls were not returned. Letter sent in Oct. no response. Certified letter sent 1/14/2010. Signed by 3rd party on 1/19/10. Survival status was obtained 6/28/11.
2.	Subject survival status	Confirmed as alive Date of last contact: 28/Jun/2011 Type of contact: Patient

This patient was randomized on 20jul2009 and did not return for the first follow-up visit. While it is unfortunate and a threat to study validity to have such an early dropout, the site appears to have followed up appropriately and documented its actions reasonably. The date JNJ provided for this patient as the reference end date? 14jan2010. JNJ uses the latter date, the date the certified letter was sent, for its ITT analyses. For its "mITT" JNJ uses 18sep2009, i.e., an estimated end of treatment date of 19aug2009 plus 30 days, although the site reported the end of treatment date as unknown. While for this unique case JNJ's mistake shortened the duration of follow-up (and this case is in the placebo arm), using a certified letter date would be expected to lengthen artificially duration of follow-up.

The following excerpt from JNJ's documentation on the reference end date (censoring date) is an example of how JNJ's approach usually appears to have maximized the duration of follow-up.

> If both of DSDTC and DSSTDTC is partial dataset or one is partial while another is totally missing, if month is missing, replace with 12-31, if day is missing, replaced with end day of that month. Time make up with 23:59:59.

DS* variables are from the DS (disposition) dataset. DSDTC is the "Date/Time of Collection" while DSSTDTC is the "Start Date/Time of Disposition Event". There are two problems with this algorithm:

- Why should a collection date be used for an event date? The collection date is usually after the event date, sometimes long after.

- Imputing to the end of the year for a date missing month and to the end of the month for a date missing day is liberal. For most patients other follow-up dates are available such that missing date imputation is not necessary and, if absolutely needed, should be conservative so as not to overstate the extent of follow-up.

The following excerpt from another end of trial eCRF illustrates yet another problem:

1.	Did the subject complete the follow-up period?	Yes
2.	Subject survival status	Confirmed as alive Date of last contact: 12/Jul/2011 Type of contact: Patient
3.	Was the ICF addendum regarding survival status approved by the ethics committee? **NOTE: This is an old question, which has been replaced by the one below.**	
4.	Was the permission document regarding survival status approved by the ethics committee?	Not applicable
5.	Were attempts made to contact the subject, who has withdrawn the informed consent?	No Subject known to have died prior to trial termination Date of death: (b) (6)

Is this patient alive or dead? I could not find in the eCRFs further follow-up to confirm the patient's vital status. This patient had an earlier end of treatment visit after the study global end date so the study's endpoint analyses should not be affected by the end-of-study vital status ambiguity. However, the determination of whether rivaroxaban has a withdrawal problem in ACS patients, as it does in atrial fibrillation patients, is severely impacted. There are three other patients with similar end of study vital status ambiguities and other patients with post-treatment endpoint neglect.

These previous problem examples may not seem critical because their absolute numbers are small. However, for these problems and others we have limited ability to detect the problems. The data collection for the final visits was sparse, e.g., the required fields were dates and check boxes. There was no requirement to collect quantitative values such as vital signs (which we have used in other submission as a surrogate for an office visit.)

The clinical status review (CSR) eCRFs for follow-up visits did have a checkbox for "phone" or "office". However, other responses were not supported (e.g., for certified letter follow-up) and the CSR eCRF did not have a specific field for who was on the "phone" or in the "office". The CSR eCRFs had checkboxes for death, cardiac ischemic events, strokes, SAEs, etc. Simple cross checks of the fields on the CSR eCRFs show many discrepancies: There were 309 "office" visits at which "death" was checked; however, 46 of these "office" visits were for patients who otherwise were confirmed alive throughout the study. In total 61 patients counted as living had a CSR checkbox of death at some time during the study. There is a large imbalance by arm: 11 placebo, 23 2.5mg, and 27 5mg patients.

In response to my queries regarding the CSR eCRFs JNJ stated the following:

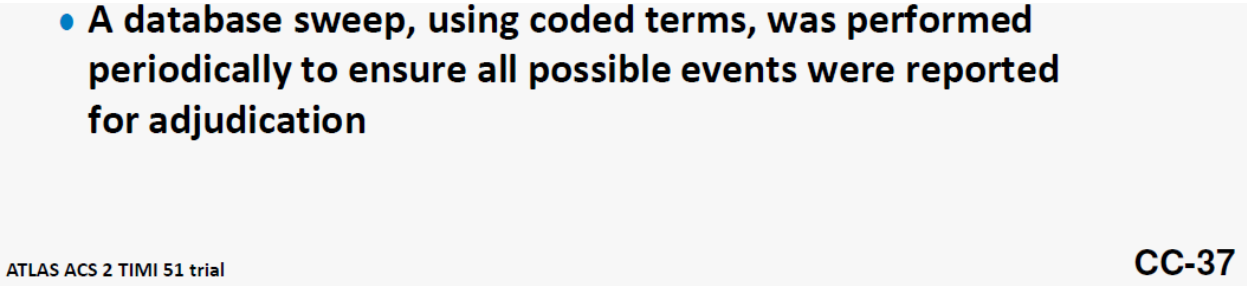
> The types of contact for "Office" versus "Phone" visits were not specifically defined. The intent of this field was to record whether or not an individual from the investigational site met with the patient in person, or spoke with them over the telephone. All visits where a death was reported should have been "Phone" visits, since an office visit would have been impossible.

and

> The collection of Clinical Status Review (CSR) data was intended to remind the sites to enter data on the appropriate pages within the eCRF. These data were not reconciled, source document verified, nor were they used within the SAP pre-specified analyses presented in the submission.

That these data, the summary eCRF on which a site could indicate that a significant event had occurred, were not reconciled and checked seems strange and contrary to the following slide from JNJ's proposed advisory committee meeting presentation.

Figure 1: Sponsor's Proposed Slide regarding "Database Sweeps" for Possible Events



I do not know how many of the problems JNJ was aware of prior to the study publication and NDA submission but JNJ's high-level description of how censoring dates were determined is illuminating:

> Last contact date will be the maximum of all available dates from the following datasets: AE, CF, CM, DS (imputed, excluding DSCAT='OTHER EVENT' and 'CODE BROKEN' record), EX (imputed), LB, RA, and SV, and the calculated date should be bounded by raw death date (see death.pdf).

Most of these datasets provide no information regarding whether the patients had suffered events or whether the possibilities of events had been checked.

COMMENT: It should not be this complicated to determine the last time a patient was contacted in a clinical trial. For a pivotal outcome trial I judge it highly concerning that one cannot determine reliably whether a subject was actually seen at an office visit vs. someone (not necessarily the patient) being contacted by phone vs. some other communication. I judge it similarly concerning that the sponsor did not follow-up on sites reporting deaths and other events on the clinical status review CRFs.

I also believe that I have identified problems with the censoring dates that JNJ uses sufficiently to justify independently estimating censoring dates. Hence I estimated censoring dates for CV endpoints based on the greatest of an event date or an office clinical status review date and censoring dates for death based on the date of death, for patients who died, or the greatest of, the CV follow-up date or the last disposition date, for patients presumed alive. Note that these censoring dates are likely still optimistic: A site could report a clinical status review in the "office" without the patient being present as evidenced by 59 office clinical status reviews performed after the date of death, one by nearly two years. I did censor these latter dates at the dates of death, but for patients without dates of death there is no simple way to verify the clinical status review dates.

Extensive Missing Follow-up, Greater in the Rivaroxaban Arms

I maintain that the most appropriate measures of the extent of follow-up are, for all cause mortality, the percentage of all randomized subjects who did not die and are not known to be alive on or after the study end date (for ATLAS the global study end date June 3, 2011) and, for CV endpoints, the percentage of all randomized subjects without CV endpoints who failed to have an assessment of CV endpoints on or after the study end date. In addition, statistics on the duration of follow-up missing in those patients with incomplete follow-up are informative for the obvious reason that we should not be as concerned about a few days of missing follow-up as we should about months. I show these percentages and statistics for JNJ's and my censoring dates in Table 4.

Table 4: Extent of Missing Follow-up in ATLAS for Sponsor and FDA Censoring Dates

	% of subjects with incomplete f/u			mean days missing		
	placebo	2.5	5	placebo	2.5	5
JNJ censoring	10	11	11	317	323	310
FDA vs f/u*	8	9	9	317	315	308
FDA cv f/u*	19	21	22	283	284	286

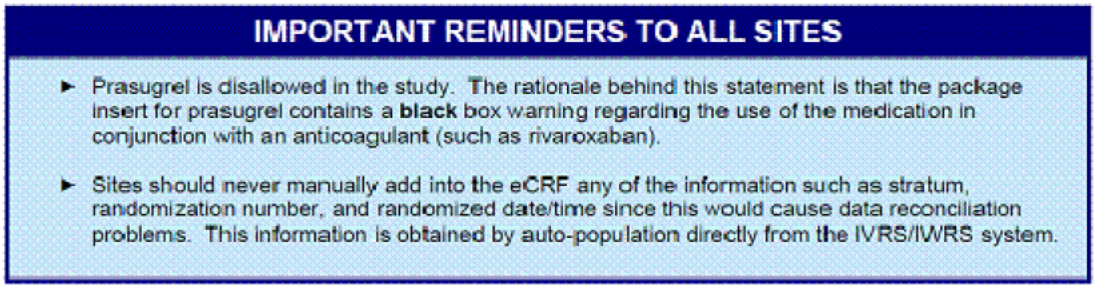
*vs f/u = vital status follow-up; cv f/u = cardiovascular endpoint follow-up

Note that the rates of subjects with missing data are greater for the rivaroxaban arms than the placebo arm and that the differences between the missing data rates are greater than the differences in endpoint rates (for mortality about 0.15 to 1%; for the primary endpoint about 0.8 to 1.2%). The missing follow-up rates are much greater than the differences in endpoint rates. For patients with missing follow-up the average amount of follow-up missing was substantial, i.e., about 10 months.

COMMENT: Because of the extent of missing follow-up in ATLAS we cannot have confidence in either the calculated mortality or CV endpoint benefits. I present other aspects of the missing data below.

Lack of Other Verification Data besides Follow-up

Follow-up data were not the only data missing from the ATLAS eCRFs. Data useful for verifying randomization were also missing. The ATLAS November 2009 newsletter to sites emphasized the following:



COMMENT: The reminder about prasugrel seems appropriate, but the instruction for sites not to enter stratum, randomization number, or randomization date into the eCRFs is strange. It should have been important for trial conduct to know whether sites had misunderstandings about any of these latter critical pieces of information. For FDA review purposes having randomization number and date/time independently recorded on CRFs by sites is valuable: Having these data independently recorded in the CRFs is one of the only guards we have against someone manipulating the randomization assignments.

Mortality Difference Not Statistically Significant

In addition to the problems with missing follow-up the mortality difference is not robust and, if deaths are counted completely, not statistically significant. I discussed the problem of three deaths not counted above. The primary clinical review also discusses an issue regarding JNJ excluding three Indian sites because of data quality issues. The results for rivaroxaban were unfavorable at these sites. While three deaths and three sites may not seem like much, they are critical for statistical significance of the mortality results as shown in Table 5.

Table 5: P Values for All Cause Mortality Both Rivaroxaban Dosages vs. Placebo by Different Death and Site Exclusions and Censoring Approaches in ATLAS

censor	strata:	both				thienopyridine			
	exclude 3 deaths:	yes		no		yes		no	
	exclude 3 sites	yes	no	yes	no	yes	no	yes	no
JNJ	"mITT" (on rx + 30d)	0.044	0.055	0.055	0.071	0.029	0.036	0.039	0.048
	ITT	0.082	0.097	0.102	0.119	0.043	0.052	0.055	0.066
FDA	ITT	0.081	0.096	0.101	0.118	0.042	0.051	0.054	0.067

It is necessary to exclude both the 3 deaths and the 3 sites in order for JNJ's primary analysis of mortality to be statistically significant. Without the exclusions the p value is 0.071. For the analysis that we had pre-specified as the preferred analysis, i.e., the ITT analysis in both strata, the p value is remote from significance, i.e., 0.118, the value shaded in red above.

COMMENT: For what I consider to be the primary mortality analysis the p value is insignificant (0.118), although the hazard ratio is still favorable for rivaroxaban (0.87). However, we cannot dismiss a mortality benefit entirely because of these subgroup analyses: The mortality difference is highly favorable (e.g., p values with two zeroes after the decimal point) for rivaroxaban 2.5 mg regardless of which of the above variations is analyzed while the mortality results for 5 mg are neutral. While statistical purists might argue that these subgroups should not be analyzed because of the failure of the primary analysis, they are pre-specified ones that were part of the study design. There are also reasonable clinical hypotheses regarding why the lower dose might

be more effective than the higher dose, e.g., more bleeding in the 5 mg group leads to more bleeding complications and more CV complications (the latter a consistent finding in all ACS trials.). The critical question is which are the better estimates of the effect of rivaroxaban upon mortality, the overall study results or the results in the 2.5 mg arm? I discuss other aspects of the mortality effect below.

Mortality Differences Not Explained by Causes of Death

I show my classification of causes of death, made without reference to arm, in Table 6.

Table 6: FDA Classification of Causes of Death in ATLAS

	placebo	2.5	5
arrhythmia	4	1	3
bleed, non-ICH*	0	0	6
cancer	13	11	12
heart failure	16	9	22
myocardial infarction	25	22	34
pulmonary embolism	2	0	0
renal failure	2	0	0
revascularization	5	4	2
sepsis	4	3	14
stroke, ICH*	5	7	6
stroke, ischemic	4	1	4
sudden	98	68	72
suicide	1	0	1
trauma	4	2	3
unknown	1	3	5
vascular	1	2	2

*ICH = intracranial hemorrhage

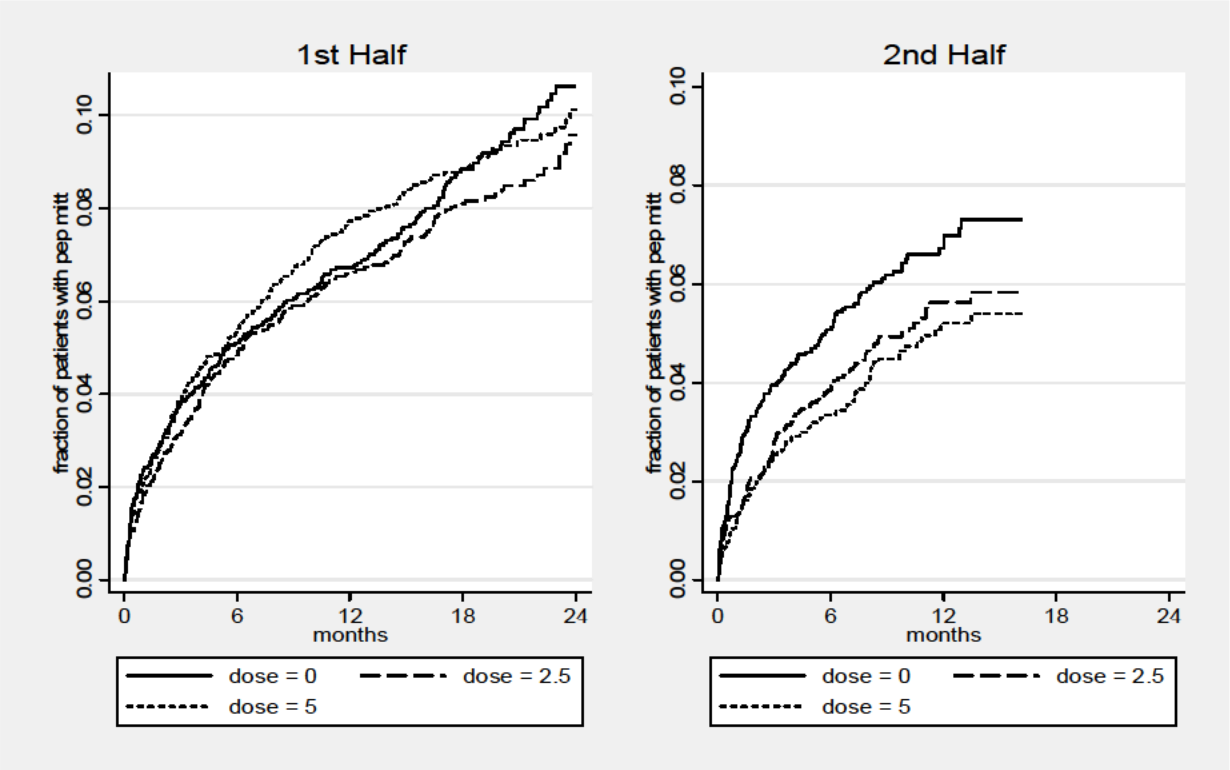
Note that the one cause of death that is dramatically lower in both rivaroxaban arms is sudden death. JNJ's classification of sudden death is similarly dramatically lower, i.e., 93 vs. 66 vs. 68. (I assigned more deaths to the "sudden" category rather than to a definite cause, e.g., I classified a sudden death that was a suspected pulmonary embolism but without documentation of a pulmonary embolism as a sudden death rather than a pulmonary embolism.) Stroke deaths are neutral across arms while MI deaths are slightly lower to neutral at 2.5 mg but higher at 5 mg. Heart failure deaths are also lower at 2.5 mg but higher at 5 mg. Bleeding deaths, although uncommon, are highest in the 5 mg arm. Why the sepsis death rate in the 5 mg arm is high is unclear, although sepsis deaths were typically pneumonia, sometimes in the setting of heart failure, or post-op complications.

COMMENT: I don't judge this pattern of deaths to provide a clear explanation of why death rates are low in the 2.5 mg arm but about equal in the placebo and 5 mg arms. I am concerned that the one category that is dramatically lower in the rivaroxaban arms, sudden deaths usually at home with little other documentation, are the ones most likely to be subject to under-reporting or missing follow-up.

Endpoints by Enrollment Half and Informative Censoring

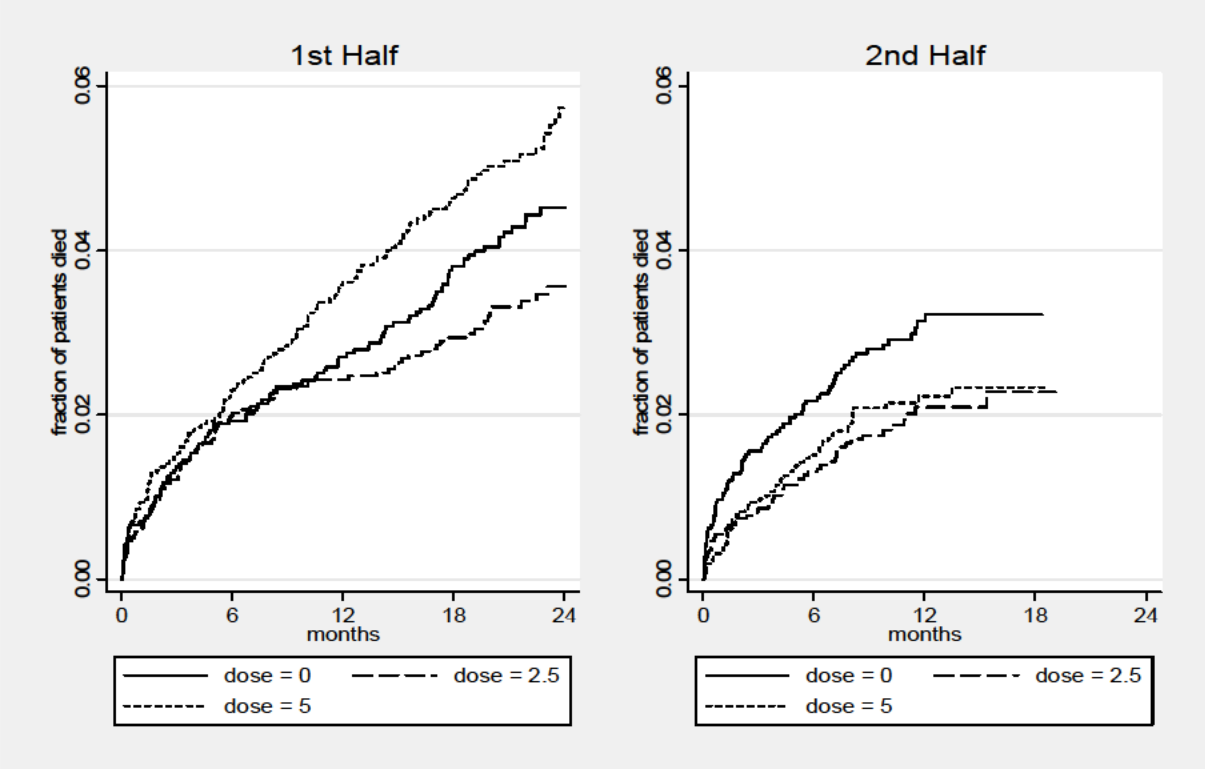
We regularly check the endpoint results in CV outcome trials during the enrollment period, e.g., starting with comparing the results for the first half of enrollment to the second. (We define enrollment half as half of the total enrollment, not half by date. ATLAS reached half of its total enrollment on February 4, 2010.) Doing so for ATLAS for the sponsor's primary analysis produces the graphs shown in Figure 2.

Figure 2: Sponsor's Primary Endpoint mITT by Enrollment Half in ATLAS



Rivaroxaban appears to have performed better for the second half patients, particularly early. Correspondingly first half placebo patients appear to have done poorly late. The results by enrollment half for mortality are a variation of these patterns as shown in Figure 3.

Figure 3: All Cause Mortality by Enrollment Half in ATLAS



The variation is that rivaroxaban 5 mg performed poorly in the first half patients and 2.5 mg performed well for them while both appear favorable for second half patients. The interaction between treatment and enrollment half for mortality is borderline significant as shown in Table 7.

Table 7: Interaction between Treatment and Enrollment Half for Mortality in ATLAS

```
Cox regression -- Breslow method for ties

No. of subjects =        15526                     Number of obs    =     15526
No. of failures =          504
Time at risk    =  249410.4667
                                                   LR chi2(3)       =     11.44
Log likelihood  =   -4722.9344                     Prob > chi2      =    0.0095

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        1.rx |   .9909782   .1160786    -0.08   0.938     .7876953    1.246723
     1.half2 |   1.006137   .1539502     0.04   0.968     .7454424    1.358003
             |
    rx#half2 |
        1 1  |   .6897074    .132242    -1.94   0.053     .4736512    1.004318
------------------------------------------------------------------------------
```

While these are subgroup analyses that could significant by chance, I did search for factors that might explain the patterns. I could not identify any baseline factors that were imbalanced among

the six dose-enrollment half subgroups. There were lower fractions of patients with histories of MI (29 vs. 25%), heart failure (13 vs. 9%), and stroke (2.3% vs. 1.4%) and unstable angina as the index event (26 vs. 22%) enrolled in the second half with roughly balanced fractions by dose in each half. PCI for the index event was slightly more frequent in the second half (59 vs. 61%).

COMMENT: These small differences in patient baseline factors would not appear to account for the different endpoint results by half. If anything, the patient CV risk (per histories of MI, heart failure, and stroke) in the second half appears lower. I cannot propose a simple reason why rivaroxaban should perform better in lower CV risk patients.

Regional site participation shifted somewhat from half 1 to half 2. Latin American sites increased enrollment about 3-fold to 8.6% and Asian sites about 40% to 12% while Eastern European sites decreased enrollment 33% to 16%. Western European enrollment was low (about 7%) and steady and US enrollment was small and declined (2.7 to 1.7%).

In the larger regions with the increases there was no clear differentiating pattern in endpoint rates. The Eastern European region did have more favorable rates for the 2.5 mg group in half 2 as did the Asia but Latin American was relatively neutral in both halves. All regions except Western Europe had more favorable results for 5 mg in half 2.

COMMENT: These regional changes are varied enough to be hard to interpret. With the exception of the decline in the Eastern European contribution, the enrollment pattern seems typical of recent CV outcome trials, i.e., decreasing enrollment in the US and increasing enrollment in Asia and less prosperous regions.

While changes in baseline factors don't explain the differences in results by enrollment half, a very good question is whether informative censoring could. I would expect informative censoring for dropouts in ATLAS, or any other ACS trial of an anticoagulant or antiplatelet agent, for the following reason: These agents cause bleeding that leads to both study drug discontinuations and dropouts short term and worse outcomes long term. It is easy to document this assertion with data from ATLAS. I show bleeding rates by follow-up status in Table 8.

Table 8: TIMI Major/Minor Bleeding Rates per 100 PEY* by Follow-up Status in ATLAS

	CV follow-up	
	incomplete	complete
placebo	3.1	0.9
2.5	6.3	1.4
5	9.0	1.8

*PEY = person exposure year

TIMI minor or greater bleeding rates are 3-5 times higher in subjects with incomplete follow-up than those with complete follow-up. I would expect these estimates to be low because, in patients who withdraw consent because of bleeding, we cannot be confident that the bleeding events were recorded.

Table 9: Myocardial Infarction and Mortality Rates by TIMI Major/Minor Bleeds in Subjects with Good CV Follow-up in ATLAS

	myocardial Infarction		death	
bleed:	no	yes	no	yes
placebo	6%	21%	6%	21%
2.5	5%	11%	6%	15%
5	5%	16%	5%	26%

Mortality rates are much higher, about five-fold, in patients who had a bleed vs. those who did not. Furthermore, only about 56% of the deaths were attributed to a cause related to bleeding (ICH bleed, other bleed, trauma). MI rates are also higher, two to three-fold, in patients who had a bleed.

COMMENT: These findings, that bleeding is associated with later MIs and deaths, are also typical of ACS trials of antiplatelet agents. That bleeding leads to both withdrawals and to CV outcome events, i.e., informative censoring, is a specific example of one of the reasons why true ITT analyses are preferred for clinical trials over on-treatment analyses, such as JNJ's "mITT" (really on-treatment plus 30 days). The second problem with ATLAS is that, with the high rates of missing data, we have no way of estimating how large an impact the informative censoring could have on the results.

These bleeding analyses show that informative censoring likely occurred in ATLAS but the above analyses do not explain directly the enrollment half results. I have done preliminary analyses of bleeding by enrollment half but my preliminary analyses are not informative, possibly because the numbers of major/minor bleeding events per arm are small and hence there is substantial variability in any estimates. I plan to do additional analyses regarding bleeding prior to the advisory committee meeting.

The one baseline cardiovascular risk factor that is a significant predictor of events, quantitative, and recorded reliably is age. I show in Table 10 the mean age by vital status follow-up and enrollment half.

Table 10: Mean Age by Vital Status Follow-up and Enrollment Half in ATLAS

	bad VS* follow-up		good VS* follow-up	
	1st half	2nd half	1st half	2nd half
placebo	62.9	61.7	61.9	62.0
2.5	62.5	64.0	62.5	62.1
5	62.0	62.7	62.6	62.3

*VS = vital status

The one number that stands out is the higher mean age of patients in the 2.5 mg arm for the second half. The mean age in the 5 mg arm for the second half is also higher than the mean age in the placebo arm and the mean age for patients with good follow-up.

COMMENT: The older mean age of the rivaroxaban patients with incomplete vital status in the second half may contribute to the apparent benefit of rivaroxaban in the second half. The impossibility of proving that informed censoring is responsible for all of the endpoint differences

in the second half (or the whole study) results from our not knowing all or even the important reasons for the informative censoring.

Insignificant Site-Reported Endpoint Results

JNJ's primary analyses are based on endpoints adjudicated by a central, blinded-to-treatment endpoint committee. Adjudication is a two-edged sword: While it should help to eliminate noise from variable site descriptions of events, it also typically introduces a single control point (the preparation of adjudication packages) manned by the sponsor at which a single individual could bias the results. For other outcome trials I have found that the central event committees adjudicated fairly based on what they were given. Contrawise, I have in the past documented problems with forwarding of cases for adjudication. Hence I assert that analyzing the events as reported by the sites, without the central adjudication, is valuable for understanding the robustness of the adjudicated results.

ATLAS had two different types of CRFs that provide information on what the sites believed were events:

- Sites indicated on "clinical status review" CRFs whether the subjects had suffered an event since the last visit. The limitations of these clinical status reviews are that the sites indicated possible events, they could not enter dates, and they could not differentiate the types of cardiac ischemic events, e.g., MI, unstable angina, etc. JNJ has stated that they did not quality audit these CRFs.

- Sites also completed event CRFs on which they provided basic information about the events including their descriptions and event dates. Sponsor monitors did interact with the sites to improve or otherwise change the descriptions, so these records are not free of sponsor influence.

I show in Table 11 the odds ratios for the clinical status reviews and in Table 12 the hazard ratios for the site-reported endpoints.

Table 11: ITT Odds Ratios of Site-Reported Clinical Status Reviews in ATLAS

	both doses vs. placebo				2.5 mg vs. placebo				5 mg vs. placebo			
	entire study		thienopyridine stratum		entire study		thienopyridine stratum		entire study		thienopyridine stratum	
	OR	p	OR	p	OR	p	OR	p	OR	p	OR	p
death	0.95	0.5	0.91	0.29	0.80	0.04	0.75	0.01	1.1	0.4	1.1	0.5
cardiac ischemic event	0.94	0.17	0.94	0.22	0.96	0.084	0.96	0.11	0.99	0.5	0.99	0.6
revascularization	0.97	0.6	1.0	>0.9	0.97	0.6	1.0	>0.9	0.98	0.7	1.0	>0.9
stroke	1.0	>0.9	1.0	>0.9	0.89	0.5	0.92	0.7	1.1	0.5	1.1	0.5

OR = odds ratio by logistic regression

Table 12: ITT Hazard Ratios of Site-Reported Endpoints and FDA CV Death in ATLAS

	both doses vs. placebo				2.5 mg vs. placebo				5 mg vs. placebo			
	entire study		thienopyridine stratum		entire study		thienopyridine stratum		entire study		thienopyridine stratum	
	HR	p	HR	p	HR	p	HR	p	HR	p	HR	p
primary endpoint*	0.89	0.093	0.89	0.11	0.87	0.074	0.87	0.079	0.92	0.3	0.92	0.3
FDA CV death	0.83	0.065	0.80	0.028	0.73	0.009	0.67	0.002	0.94	0.6	0.93	0.5
myocardial infarction	0.91	0.33	0.93	0.4	0.94	0.6	0.94	0.6	0.90	0.3	0.92	0.4
stroke	1.2	0.3	1.3	0.2	1.1	0.7	1.2	0.8	1.4	0.1	1.3	0.2

HR = hazard ratio by Cox regression; *primary endpoint = time to first CV death per Table 6 or site-reported MI or stroke

The analyses in Table 11 and Table 12 are ITT analyses, i.e., censored no later than the global study end date, using all sites and all reported deaths. I did interpret and check CRFs and adjudication packages for some site-reported events because sites not infrequently reported events vaguely or misspelled. I did use both original and final site verbatim terms for events to try to minimize the sponsor influence. I did not use the site-reported causes of death because sites classified many deaths as "unknown" (122) despite having additional information regarding them. For CV deaths I used the classification in Table 6, counting unknown deaths as CV deaths and non-ICH bleeding deaths as non-CV. I based the hazard ratios for the non-primary endpoints in Table 13 on times to any first event, not the times to the corresponding component of the primary endpoint.

Rivaroxaban is not statistically significantly superior to placebo for any comparison of both doses to placebo for the entire study or for any analysis of the primary endpoint. On the other hand, the point estimates of the hazard ratios are favorable for rivaroxaban except for stroke. The one highly favorable result is for CV death for 2.5 mg alone vs. placebo.

COMMENT: By these analyses rivaroxaban is not superior to placebo except for the isolated finding of better CV mortality for 2.5 mg vs. placebo. There are four problems casting doubt on the validity of this superiority:

- *Mortality for 2.5 mg vs. placebo is a subgroup analysis when it is unclear whether the primary analysis succeeded. While the mortality results for 2.5 mg are impressive and mortality is always an outcome of interest in CV trials, it is possible that the superiority for 2.5 mg for mortality is a chance subgroup finding.*

- *It is strange that 2.5 mg wins on CV mortality while losing on stroke and being relatively neutral for all MIs. This strangeness is also reflected in the causes of death shown in Table 6.*

- *Vital status is missing for 8-9% of the patients, far greater than the differences between the placebo and 2.5 mg arms for either CV mortality (0.85%) or all cause mortality (1.0%). Follow-up was also poorly documented.*

- *The analyses of bleeding and enrollment half suggest that there were problems with informative censoring.*

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/s/

THOMAS A MARCINIAK
04/26/2012

CLINICAL PHARMACOLOGY REVIEW

NDA	202-439, S_02
Submission dates	12/29/2011, 2/3/2012
Brand name	Xarelto®
Generic name	Rivaroxaban
Dose and dosage form	2.5 mg film coated immediate release tablet
Proposed indication	Reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) [STEMI/NSTEMI/UA] in combination with aspirin alone or with aspirin plus a thienopyridine (clopidogrel or ticlopidine).
Sponsor	Janssen Pharmaceuticals Inc
Submission type	Priority
Reviewers	Divya Menon-Andersen, PhD
	Dhananjay Marathe, PhD
Pharmacometrics Team leader	Yaning Wang, PhD
Team leader	Rajanikanth Madabushi, PhD

Table of contents

1 EXECUTIVE SUMMARY

Janssen Pharmaceuticals Inc. has developed 2.5 and 5 mg dose strengths of the oral factor Xa inhibitor (FXa) rivaroxaban for use in acute coronary syndrome (ACS), and is seeking an indication for risk reduction of thrombotic cardiovascular events in patients with ACS (STEMI/NSTEMI/UA) in combination with aspirin alone or with aspirin plus a thienopyridine (clopidogrel or ticlopidine). Rivaroxaban is currently indicated for (1) risk reduction in stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF, 20 mg) and (2) prophylaxis of deep vein thrombosis (DVT) in patients undergoing knee or hip replacement surgery (10 mg).

In this submission, the sponsor submitted a Phase 2 dose ranging study (ATLAS ACS TIMI 46) and a single pivotal Phase 3 efficacy and safety study (ATLAS ACS 2 TIMI 51). Both ATLAS ACS TIMI 46 and ATLAS ACS 2 TIMI 51 enrolled subjects with a recent ACS event, who were receiving aspirin alone or aspirin plus a thienopyridine. The studies were stratified based on the intention to use a thienopyridine. Total daily doses ranging from 5 to 20 mg, administered as a once or twice daily regimen, were evaluated in TIMI 46, a fixed duration study. ATLAS ACS 2 TIMI 51 was an event driven trial in which two doses of rivaroxaban, 2.5 and 5 mg, administered twice daily, were evaluated and compared against placebo in the background of standard of care therapy (aspirin or aspirin plus a thienopyridine).

Clinical Pharmacology and Biopharmaceutics findings relevant to the ACS indication were reviewed and are presented in this document. Please consult previous reviews by Dr. Grillo (DARRTS date 04/06/2009), and Dr. Sabarinath (DARRTS date 08/10/2011) for detailed clinical pharmacology information on rivaroxaban pertaining to the DVT and AF indications, respectively.

1.1 Recommendations

From a Clinical Pharmacology perspective the submission is acceptable.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

General pharmacokinetics

As established in earlier submissions, peak plasma rivaroxaban concentrations are observed within 2 to 4 hours of oral administration of rivaroxaban tablets. In the dose range evaluated in the Phase 3 study, rivaroxaban exhibits dose proportional kinetics with close to 100% bioavailability and is not affected by food. The elimination half-life of rivaroxaban is about 6 to 8 hours in young healthy subjects and increases to 11 to 13 hours in the elderly. Rivaroxaban is a substrate of the efflux transporters P-gp and BCRP. About 50% of an orally administered dose is metabolized in the liver, mainly by CYP3A4/5. Rivaroxaban is excreted mainly in urine (~ 66%), of which about half (~36% of administered dose) is excreted as unchanged drug.

Exposure – outcomes relationships

Clinically significant bleeding, the primary safety endpoint in the Phase 2 dose ranging study, increased with increasing dose/exposure. There were no trends observed in any of the efficacy endpoints with increase in dose.

Dose reduction in subjects with moderate renal impairment

The trend for efficacy at the 2.5 mg BID dose is consistent across all renal function categories while there appears to be a trend towards increased bleeding in patients with moderate renal function. However, any dose adjustment in this group aimed at reducing the number of bleeding events may result in loss of efficacy. Hence, dose adjustment to less than 2.5 mg BID is not feasible.

2 QUESTION BASED REVIEW

This is an abbreviated version of the QBR. Please refer to the OCP review by Dr. Grillo (DARRTS date 04/06/2009) for the detailed QBR.

2.1 General Attributes of the Drug

Rivaroxaban is a selective oral FXa inhibitor that is currently approved for use in prevention of stroke in patients with AF and for prophylaxis in DVT. The sponsor is seeking approval of rivaroxaban for use in ACS. The development program was conducted under IND 75931.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Please refer to the OCP review by Dr. Grillo for physical-chemical properties of the drug substance.

Rivaroxaban 2.5 mg tablets are round, light yellow, biconvex, film coated tablets. The dosage strengths used in the ACS program were compositionally similar to the 10 mg strength that is currently being marketed. A biowaiver was requested for the 'to be marketed' 2.5 mg dose strength and will be addressed by ONDQA Bipharmaceutics.

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Rivaroxaban is a selective, direct acting oral FXa inhibitor. Factor Xa plays a central role in the coagulation cascade. It is hypothesized that adding an anticoagulant to anti-platelet therapy will enhance prevention of atherothrombosis and result in reduced subsequent ACS events.

The proposed indication is risk reduction of thrombotic cardiovascular events in patients with ACS (STEMI/NSTEMI/UA) in combination with aspirin alone or with aspirin plus a thienopyridine (clopidogrel or ticlopidine).

2.1.3 What are the proposed dosages and routes of administration?

The sponsor is seeking approval of rivaroxaban 2.5 mg tablets, to be administered orally twice daily. For the AF and DVT indications, rivaroxaban is approved at higher doses of 20 mg and 10 mg respectively, to be administered orally once daily.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

The clinical program for rivaroxaban in ACS consisted of a Phase 2 dose ranging study and a pivotal Phase 3 efficacy and safety study. Salient features of both studies are listed in **Table 1**.

Table 1 Salient features of clinical studies

Study	Population	Treatment groups	Endpoints
ATLAS ACS TIMI 46 Phase 2 dose ranging study	Recent ACS (STEMI, NSTEMI, or UA) receiving background aspirin therapy with or without the intention to use a thienopyridine	ASA alone (stratum 1), n = 761 Placebo, 2.5 mg BID, 5 mg QD, 5 mg BID, 10 mg QD, 10 mg BID, 20 mg QD ASA+thienopyridine (stratum 2), n = 2730 Placebo, 2.5 mg BID, 5 mg QD, 5 mg BID, 10 mg QD, 7.5 mg BID, 15 mg QD,10 mg BID, 20 mg QD	Pharmacokinetic Sparse sampling in all study subjects and rich sampling in a subset in all dose groups Pharmacodynamic Sparse sampling in all study subjects (prothrombin time and anti Factor Xa activity) Efficacy Composite of first occurrence of all cause death, MI, stroke, severe recurrent ischemia requiring revascularization Safety Clinically significant bleeding (TIMI major, TIMI minor and bleeding requiring medical attention)
ATLAS ACS 2 TIMI 51 Phase 3	Recent ACS (STEMI, NSTEMI, or UA) receiving background aspirin therapy with or without the intention to use a thienopyridine	ASA alone (stratum 1) n=1053 Placebo, 2.5 mg BID, 5 mg BID ASA+thienopyridine (stratum 2) n=14473 Placebo, 2.5 mg BID, 5 mg BID	Efficacy Composite of first occurrence of CV death, MI, stroke Safety Non-CABG TIMI major

Note: All analyses presented in this review pertain to Stratum 2.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical studies?

In the Phase 2 dose ranging study, the primary efficacy endpoint was a composite of first occurrence of all cause death, myocardial infarction (MI), stroke and serious recurrent ischemia requiring revascularization. The primary safety endpoint was clinically significant bleeding (CSB) (includes TIMI major, TIMI minor and bleeding requiring medical attention). Similarly, in the Phase 3 trial, a composite of first occurrence of cardiovascular death (CVD), myocardial infarction (MI) and stroke, and non-CABG TIMI major bleeding were the primary endpoints for efficacy and safety, respectively.

Following an ACS event, patients are at a high risk of MI, stroke or CVD. Therefore, these are meaningful endpoints in evaluating a drug hypothesized to reduce the incidence of subsequent ACS events/stroke/CVD. Please refer to the medical officer's review for information pertaining to determination of endpoint events.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Rivaroxaban is the only active moiety in plasma and was appropriately identified and measured in plasma in ATLAS ACS TIMI 46.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for safety and efficacy?

A dose-dependent increase was observed in CSB, the primary safety endpoint in the Phase 2 dose ranging study. The observed trend in the data suggests that this increase is monotonic. As seen in **Figure 1**, CSB was higher at all doses/dosing regimens of rivaroxaban when compared to placebo (background of ASA + clopidogrel). Additionally, in the Phase 3 trial, a trend towards increased bleeding was observed at the higher dose (5 mg vs 2.5 mg HR(95% CI) 1.27 (0.91, 1.77)).

There were no trends observed in any of the efficacy endpoints with increasing dose. The Phase 2 study was not adequately powered to inform dose/dosing regimen – efficacy relationship. As a consequence of this, dose/exposure response relationships cannot be established.

In the Phase 3 trial no further increase in effect was observed at 5 mg BID (5 mg vs 2.5 mg HR(95% CI) 1.02 (0.87, 1.21)), suggesting a flat dose-response relationship in the dose range evaluated.

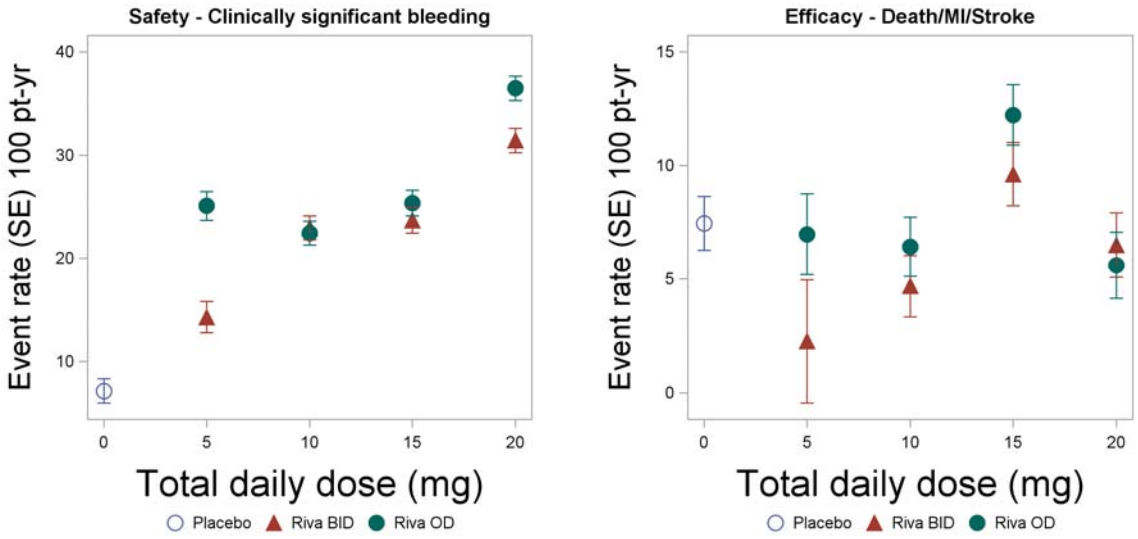


Figure 1 Clinically significant bleeding (*left panel*) increases with increasing doses, while the efficacy endpoint of death/MI/stroke (*right panel*) appears to be dose independent. The study was not adequately powered to inform efficacy (**ATLAS ACS TIMI 46, Stratum 2**).

Pharmacokinetic samples were collected in all subjects in ACS TIMI 46 following a sparse sampling scheme. However, sufficient number of observations at pre-determined time points such as C_{max} or C_{trough} were not available to reliably determine exposure-response relationships (for instance, all samples to be collected at pre-dose on day 180 for the QD regimens were collected at ~ 12 h post dose). This limits determination of exposure-response characteristics for rivaroxaban.

2.2.4.2 Is the dose and dosing regimen selected for ATLAS ACS 2 TIMI 51 appropriate?

The dose and dosing regimen selected to be tested in Phase 3 appear to be reasonable.

Dose selection for Phase 3 was primarily driven by the safety findings in the Phase 2 study. A dose/concentration dependant increase in CSB was observed in the dose ranging study. As seen in **Figure 1** amongst all the dose/dosing regimens tested, the incidence of CSB was the lowest at 2.5 mg BID and was therefore a reasonable choice. A minimum of three fold increase in the risk for CSB, compared to placebo (ASA+clopidogrel) was observed at all other doses. The choice to study 5 mg BID as against 5 mg QD (similar CSB) was therefore most likely determined by the need to have a second dose that provided systemic exposure greater than 2.5 mg BID (in the absence of any information on efficacy) and also the ease/practicality of conducting a large study with the same dosing regimen.

2.2.5 What are the PK characteristics of the drug?

Please refer to the OCP review by Dr. Grillo for the pharmacokinetic characteristics of the drug.

2.2.5.1 How does the PK of the drug and its major metabolites in the ACS population compare to that in healthy subjects?

The pharmacokinetics of rivaroxaban in the ACS population is similar to that reported in healthy subjects.

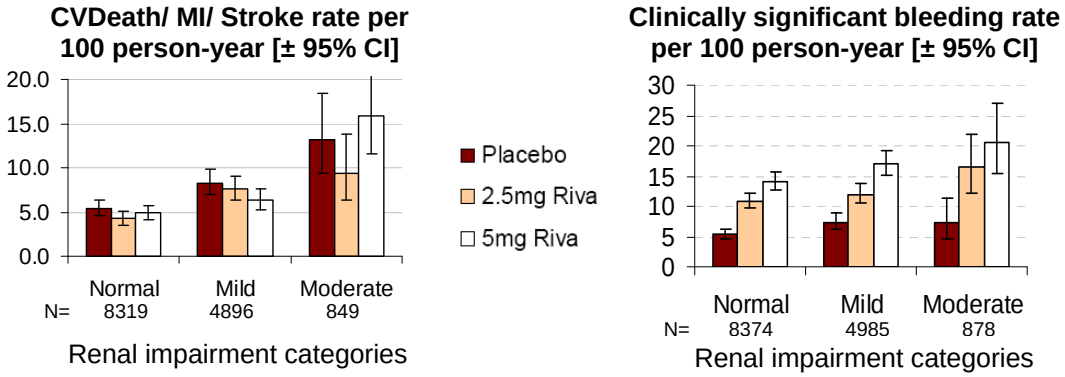
In ATLAS ACS TIMI 46, pharmacokinetic data following intensive sampling were available in a small subset of patients at all dose levels. At steady state, peak plasma rivaroxaban concentrations were observed within 2 to 4 h post dose. Mean total clearance (±SD) was estimated to be about 11 (±2.8) L/h in the ACS population and is similar to that reported in healthy subjects (10.8 (±1.3) L/h[1]).

2.3 Intrinsic Factors

2.3.1.1 How does the risk benefit profile for patients with moderate renal impairment compare to patients with normal renal function? Is a dose adjustment required?

As seen in **Figure 2** ***bottom panel***, with 2.5 mg BID, the trend for efficacy is consistent across all renal function categories while there appears to be a trend towards increased bleeding in patients with moderate renal function. However, any dose adjustment in this group aimed at reducing the number of bleeding events may result in loss of efficacy. Hence, dose adjustment to less than 2.5 mg BID may not be feasible.

An approximately 50% increase in total systemic exposure to rivaroxaban has been observed in subjects with moderate renal impairment[2]. No dose adjustments were made in this population in either Phase 2 or Phase 3 trial. Of the subjects enrolled in stratum 2 of the Phase 2 study only 2.6% had moderate / severe renal impairment (CrCL < 50 mL/min). About 6% of subjects enrolled in stratum 2 of the Phase 3 study had mild to moderate renal impairment (30 -80 mL/min) and therefore data from the phase 3 trial were used to evaluate the impact of renal function on the effect of rivaroxaban (**Figure 2**). Patients with severe renal impairment were excluded from the Phase 3 trial.



[1] *Study number BAY59-7939/10842, NDA 22-406*

[2] *Xarelto, US package insert*

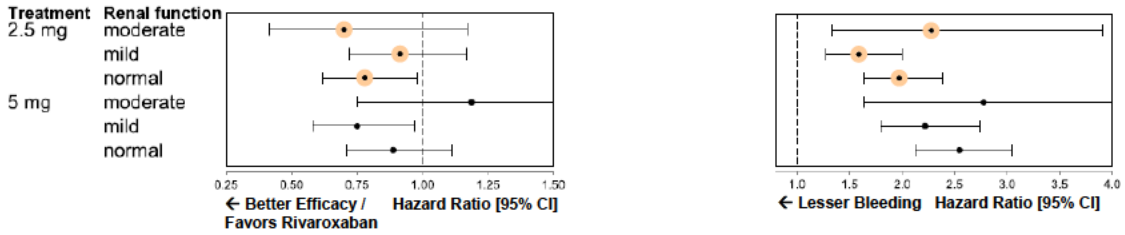


Figure 2 Efficacy and bleeding profile indicate that a dose adjustment in patients with moderate renal impairment is not required. *Top panel:* Incidence of efficacy and bleeding events by renal function category. *Bottom panel:* Unadjusted hazard ratios for efficacy and safety endpoints by renal function category for rivaroxaban treatment against placebo (**ATLAS ACS 2 TIMI 51, Stratum 2**).

2.4 Analytical Section

Rivaroxaban was identified and measured in ATLAS ACS TIMI 46 using a validated LC/MS/MS method. The assay method was previously reviewed and judged to be acceptable (NDA 22-406).

The performance of the assay method during study sample analysis satisfied all criteria for 'application to routine analysis' set by the Bioanalytical Guidance, and was therefore acceptable.

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/s/

DIVYA MENON ANDERSEN
04/23/2012

DHANANJAY D MARATHE
04/23/2012

YANING WANG
04/24/2012

RAJANIKANTH MADABUSHI
04/24/2012